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

Linda Booij[1], Cees A. Swenne[2], Jos F. Brosschot[1], P.M. Judith Haffmans[3], Julian F. Thayer [4], and A. J. Willem Van der Does[1,5]

1 Department of Psychology, Leiden University, the Netherlands

2 Department of Cardiology, Leiden University Medical Center, the Netherlands

3 Psychomedical Center Parnassia, The Hague, the Netherlands

4 Personality and Cognition / NIA, Gerontology Research Center, Baltimore, USA

5 Department of Psychiatry, Leiden University Medical Center, the Netherlands

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Address for correspondence:

A.J.W Van der Does, PhD

Department of Psychology; Leiden University

Wassenaarseweg 52; 2333 AK Leiden, The Netherlands

Phone: + 31 71 527 3377 Fax: + 31 71 527 4678 vanderdoes@fsw.leidenuniv.nl

Abstract

Background: Depression is a major risk factor for cardiovascular disease (CVD). An important risk factor for CVD - low Heart Rate Variability (HRV) - has often been found in depressed patients, and has been associated with impulsivity. The present study investigated whether experimental lowering of serotonin would decrease HRV 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 (ATD) in a randomized counterbalanced double-blind crossover design. HRV and impulsivity were assessed during each ATD 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 ATD led to a larger increase in depressive symptoms than low-dose ATD. High-dose ATD decreased HRV and increased impulsivity and anxiety, but only in patients with a history of suicidal ideation. Symptom effects of high-dose ATD correlated with low HRV at baseline.

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

Introduction

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 having the ability to establish causal relationships between serotonin levels and behavior (Young et al., 1985).

It has frequently 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). ATD has also 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 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 patients who had no history of suicidal ideation (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 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 has repeatedly 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 has also been observed in anxiety disorders (Thayer et al., 1996; Friedman and Thayer, 1998) and in

impulse-control disorders, including attention deficit hyperactivity disorder (Beauchaine et al., 2001), substance abuse (Ingjaldsson et al., 2003), psychosis (Valkonen-Korhonen et al., 2003) and in healthy highly-hostile individuals (Sloan et al., 2001; Demaree and Everhart, 2004). 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). Importantly, HRV has been associated both structurally and functionally with activity of the prefrontal 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 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 might 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. While it is widely accepted that lowered 5-HT levels negatively influence mood and behavior, it has only recently become evident 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, as this reflex reacts to any blood pressure increase/decrease by a heart rate decrease/increase. Beat-to-beat blood pressure changes are present in any person, even in a stable hemodynamic stituation, 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). Serotonin-depleted baroreflex function might decrease 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 suicidal ideation as compared to 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 suicidal ideation 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/aggressive behavior, history of suicidal ideation was used as an index for individual differences in impulse control. Although other conditions would also imply underlying impulsivity, e.g. a history of substance abuse or a cluster B personality disorder, such markers would interfere with our aim to study ATD in *remitted* patients with a *primary* diagnosis of major depressive disorder.

We assessed HRV on three occasions, and at each occasions during rest (baseline) and during cognitive testing, in particular the continuous performance test (CPT). Changes in impulsivity following ATD were measured by the CPT (Nuechterlein, 1991; Cornblatt et al., 1989; Keshaven et al., 2003). As in our previous studies, two different 'dosages' of ATD were used (25.7 g *vs*. 102.5 g amino acids), aimed at reducing plasma Trp levels by 40-50 %, and 80-90 % respectively (Van der Does, 2001). Although the 25 % strength mixture was initially developed as a placebo procedure by Krahn et al. (1996), it has been shown that, in combination with a one-day low-Trp diet, it reliably leads to moderate reductions of Trp levels, 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).

Based on previous ATD studies and the reported association between depression and CVD, the following hypotheses were tested:

1) High-dose ATD will cause a larger increase in depressive symptoms than low-dose ATD;
2) High-dose ATD will reduce HRV at rest and during the CPT;

3) 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 suicidal ideation. 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: age between 18 and 65; 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 (HRSD, 17-items) (Hamilton, 1960) lower than 15 (Frank et al., 1991). Exclusion criteria were: substance abuse within last 3 months, psychosis (lifetime), major physical illness, lactation, and pregnancy. Diagnoses, demographic and clinical background variables including history of suicidal ideation during past depression were assessed with the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1995) by a psychologist and checked in medical records.

Twenty participants entered the study. One female patient dropped out prior to the afternoon assessments of the first session (high-dose ATD) because of nausea starting 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 in Table 1, separately for groups with and without suicidal ideation during past depression (SI+ *vs*. SI-).

<<Table 1 near here>>

High-Dose and Low-Dose Acute Tryptophan Depletion. 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 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 h low Trp diet (160 mg/day) prior to both sessions.

Instruments

Symptoms

Symptoms were assessed with the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1992), the Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1960); the Brief Anxiety Scale (BAS) (Tyrer et al., 1984); Beck Depression Inventory (BDI-II; Beck et al., 1996) and Positive and Negative Affectivity Scale (PANAS) (Watson et al., 1988). The latter questionnaire consists of positive (low score indicative of depression) and negative affectivity subscales (high score indicative of both depression and anxiety).

CPT

264 letters were presented one by one for 150 ms in random order, with 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 and errors were registered. The task took 8 minutes to complete. The primary outcome measure was beta (β). Beta is a measure of impulsivity; individuals with high β have the tendency to under-respond and are assumed to be cautious; low β is associated with over-responding and risk-taking behavior (Conners et al., 2003; Nuechterlein 1991). Secondary outcome measures were: d-prime (d'; a measure of accuracy, corrected by response tendency); correct responses to target stimuli (% of hits); responses to non-targets (% of false-alarms); and median reaction times (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 using EDTA tubes to determine total plasma Trp and ratio Trp/ large neutral amino acids (LNAAs). Immediately after sampling, the blood was centrifuged for

20 minutes at 2650g_{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 using 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 tips of the shoulder blades) and connected to the AMS device.

In addition to heart rate (HR), time domain measures of HRV variables included the standard deviation of the interbeat intervals (SD) and the coefficient of variation CV_r (SD/interbeat intervals) as estimates of overall HRV; 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 previously (Bootsma et al., 1994).

Procedure

The study was approved by an independent, nationally certified medical ethics committee. After providing oral and written information about the study, we obtained written informed consent from all participants.

Prior to the ATD sessions. Participants were invited to a screening session to verify in- 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 one 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 h, patients remained in a private research room. The AMS system was placed on the participants 4.5 h after the ATD drink. After a break of about 10 minutes, cardiac activity was assessed during a five minutes period, in 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 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 h after ingestion of the ATD drink. The CPT, completed at +5.5 h, was part of a larger cognitive test battery that is not further described here. After removal of the ECG 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 one week later; those who had received high-dose ATD in the first session received low-dose ATD in the second session and vice versa.

Post-intervention 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 ten minutes after the mood assessments and took place before blood sampling. The procedure was identical as during the ATD sessions. This post-intervention 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 (ANOVA) 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 measure multivariate analysis of variance (MANOVA). For the symptom scales and biochemical measures, *ATD* (low-dose *vs.* high-dose) and *time* (-

1 h, +6.5 h, +24 h) were the within subjects factors. *ATD* (baseline *vs.* low-dose *vs.* high-dose ATD) was used as within-subject factor for the CPT. *ATD* (baseline *vs.* low-dose *vs.* high-dose ATD) and *period* (rest *vs*. CPT) were the within subjects factors for the cardiovascular measures. History of suicidal ideation (serious suicidal thoughts/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 6-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 alpha may be needed to keep the probability of a type II error under control. This could cause a power problem, although the sample size of the present study is comparable with those of some other ATD studies. To correct for multiple comparisons and to still have reasonable power, we set alpha 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, as 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 post-intervention 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 post-intervention sessions as a baseline measure was checked by a 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 post-intervention session.

Results

Data Screening

One patient of the SI+ group had an extremely high false alarm rate on the CPT in the low-dose condition (22.7 %). The mean percentage 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*-residuals = |3.78|; Mahalonobis distances = 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 non-target 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.

Prior to GLM analysis, reaction time for the CPT and HF were log10 transformed and PNN50 was square root transformed to achieve a normal distribution of the data (Stevens 1996). BDI-II and PANAS scores were analyzed by means of nonparametric tests, as transformations were unsuccessful.

ATD effects on Amino Acids

The reduction in total Trp (-1 h minus +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 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 t(-1 h) to t(+ 6.5 h) in the high-dose condition was larger than the increase in the low-dose condition ($p < .01$). Eight of the nineteen patients had an increase in MADRS of at least 6 points. PANAS positive scores decreased from t(-1 h) to t(+6.5 h) after high-dose ATD compared to the low-dose ATD ($Z = -2,40$; $p = .02$), while BDI-II scores increased at the same time points ($Z = -2,28$; $p = .02$). Significant group (defined by history of suicidal ideation; SI) by ATD by time interactions were found for the BAS [$F(2,34) = 4.01$; $p = .03$], with the largest increase from t(-1 h) to t(+6.5 h) in the high-dose condition for the SI+ group [$F(1,17) = 7.21$; $p = .016$].

Changes in PANAS negative scores 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 towards 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 suicidality. Overall, symptoms 24 h after ATD had returned to baseline levels (data not shown).

<<Table 2 near here>>

Effects of ATD on Cardiac Activity

GLM 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 both to baseline [$F(1,17) = 14.24$; $p = .002$] and to 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 [$F(2,34) = 6.56$; $p = .004$], HF [$F(2,34) = 4.30$; $p = .02$], but not 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 to 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 to 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.

<<Table 3 near here>>

CPT

Practice effects. There were no significant differences in CPT performance between the post-ATD session and the screening sessions, neither 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.

ATD effects. There was no main effect of ATD on any outcome measure of the CPT. However, the group by ATD interaction for the impulsvity 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 were also 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 *vs*. 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 to 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 vs. 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 vs. low-dose, neither were there any ATD effects on percentage of false alarms.

<<Table 4 near here>>

Relation Between Baseline HRV and ATD Response

A significant correlation was found between change in MADRS during high-dose ATD (+6.5 h minus -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 6 points on the MADRS) as compared to patients with relatively high SD, RMSSD and PNN50 levels at baseline (6/9 *vs*. 2/10 patients) [$\chi 2 = 4.23$; p = .04; Fisher's exact: p = .07 (2-tailed); p = .05 (1-tailed)]. There were no differences in clinical or demographic measures between these two groups.

<<Figure 1 near here>>

Relationship between reduction in tryptophan levels and changes in HRV

Analyses of the cardiac measures and CPT were re-run, 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 ratio Trp/LNAA and ATD induced changes in any of the cardiac outcome measures.

Discussion

The present study confirmed that high dose ATD induced more depressive symptoms in remitted depressed patients than the low-dose condition (Spillmann et al., 2001; Booij et al., 2005b). The main new findings are that, in remitted patients with a history of suicidal tendencies, high-dose ATD: 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 to controls (e.g. Agelink et al., 2002; Rechlin et al., 1994), but negative studies have also been reported (see 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 which 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 six 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 (for a review see 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 seem 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, since 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 following ATD was was not larger in patients with previous suicidal ideation than in those without. However, as the sample size in the former study was much larger than in the present study, the difference may be due to 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 previously (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 based on self-reported information. On the other hand, 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 due to 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, e.g. physical fitness, dietary habits, time on medications and other types of previous treatments. On the other hand, 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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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 in years (*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 in months (*SD*)	35.5 (37.7)	13.7 (25.3)	$F(1,17) = 2.28$; $p = .15$

Note. SSRI = selective serotonin reuptake inhibitor; SSNRI = serotonin noradrenalin reuptake inhibitor.
[a] Fisher's exact; one-tailed. The relatively large number of episodes in the SI+ group was due to two patients who had more than 10 episodes. The relatively long duration of remission for the SI+ group was due to two other patients that had been in (partial) remission for about seven years.

Table 2.
Means (*SE*) of the Questionnaires 1 h before and 6.5 h after High-Dose ATD as a Function of Group.

Variable	SI + group (n = 8)		SI – group (n = 11)	
	-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)

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

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

Variable	SI + group (n = 8)		SI – group (n = 11)	
	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)

Note. HR = heart rate; SD IBI = standard deviation of interbeat intervals; CV = coefficient of variation; RMSSD = root mean square of successive differences; PNN50 = percentage of adjacent intervals that varied more than 50 ms. HF = high frequency power (0.14-0.40 Hz); LF = low frequency power (0.07-0.14 Hz).
Statistics of the low-dose condition are not shown, available upon request.

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

Variable	SI + group (n = 8)		SI – group (n = 11)	
	Baseline	High-dose	Baseline	High-dose
Beta (LN)[1]	1.94 (0.32)	1.21 (0.37)	1.83 (0.21)	2.02(0.29)
d-prime[1]	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[1]	1.32 (0.88)	0.79 (0.25)	0.46 (0.22)	0.67 (0.21)

Note. [1] SI+ group based on n = 7. Statistics of the low-dose condition are not shown, available upon request

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