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**Regular Article**

# Noradrenergic activation induced by yohimbine decreases interoceptive accuracy in healthy individuals with childhood adversity

André Schulz[1], Christian E. Deuter[2], Ion-Hideo Breden[1], Claus Vögele[1], Katja Wingenfeld[2], Christian Otte[2] and Linn K. Kuehl[2]

[1]Clinical Psychophysiology Laboratory, Institute for Health and Behaviour, Department of Behavioural and Cognitive Sciences, Faculty of Humanities, Education and Social Sciences, University of Luxembourg, Esch-sur-Alzette, Luxembourg and [2]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

## Abstract

Acute stress affects interoception, but it remains unclear if this is due to activation of the sympatho-adreno-medullary (SAM) or hypothalamic–pituitary–adrenocortical axis. This study aimed to investigate the effect of SAM axis activation on interoceptive accuracy (IAcc). Central alpha2-adrenergic receptors represent a negative feedback mechanism of the SAM axis. Major depressive disorder and adverse childhood experiences (ACE) are associated with alterations in the biological stress systems, including central alpha2-adrenergic receptors. Here, healthy individuals with and without ACE as well as depressive patients with and without ACE ($n = 114$; all without antidepressant medication) were tested after yohimbine (alpha2-adrenergic antagonist) and placebo. We assessed IAcc and sensibility in a heartbeat counting task. Increases in systolic and diastolic blood pressure after yohimbine confirmed successful SAM axis activation. IAcc decreased after yohimbine only in the healthy group with ACE, but remained unchanged in all other groups (Group × Drug interaction). This effect may be due to selective upregulation of alpha2-adrenergic receptors after childhood trauma, which reduces capacity for attention focus on heartbeats. The sympathetic neural pathway including alpha2-adrenergic circuitries may be essential for mediating interoceptive signal transmission. Suppressed processing of physical sensations in stressful situations may represent an adaptive response in healthy individuals who experienced ACE.

**Keywords:** alpha2-adrenergic receptors, childhood trauma, interoception, major depressive disorder, stress

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## Introduction

Interoception, the perception of signals from inside the body, plays an important role in health and disease. Altered interoception can be observed in mental disorders with physical symptoms, such as major depressive disorder (MDD) (Avery et al., 2014; Dunn, Dalgleish, Ogilvie, & Lawrence, 2007; Terhaar, Viola, Bar, & Debener, 2012) or somatic symptom disorders (Pollatos et al., 2011; Schaefer, Egloff, Gerlach, & Witthoft, 2014). One important factor for altered interoception and, therefore, the generation of physical symptoms in these disorders is an allostatic disturbance of regulatory circuitry of bodily systems (Harshaw, 2015; Khalsa et al., 2018; Schulz & Vögele, 2015). Two prominent examples of these regulatory circuitries concern both physiological stress axes, that is the sympatho-adreno-medullary (SAM) axis and hypothalamic–pituitary–adrenocortical (HPA) axis (Chrousos & Gold, 1992; McEwen, 2007). One way to understand symptom generation in mental disorders may thus be elucidating the impact of both stress axes on interoception.

Interoception is considered a multifaceted construct and can be subdivided into (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015): (a) *Interoceptive accuracy* (IAcc), that is the correspondence between objectively occurring and perceived bodily signals (e.g., heartbeats), which is typically assessed using heartbeat perception tasks (e.g., "heartbeat counting task" [HCT]: Schandry, 1981). (b) *Interoceptive sensibility* (IS), which refers to the tendency to focus on signals from inside the body. This facet is based on self-reports, such as confidence ratings about one's accuracy or specific questionnaires. (c) Metacognitive *interoceptive awareness*, representing the correspondence between IAcc and IS, which is estimated with intra-individual correlations between both measures, thus requiring a large number of trials to produce interpretable data (Garfinkel et al., 2015). IAcc is interpreted as the most basic indicator of interoceptive abilities as it shows a stable relationship with both other facets, whereas the other facets

**Author for Correspondence:** Linn K. Kuehl, Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany; E-mail: linn.kuehl@charite.de

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remain partially unrelated (Forkmann et al., 2016; Garfinkel et al., 2015, 2016).

IAcc increases after a strong laboratory stressor when attention is only focused on heartbeats (Schandry & Specht, 1981; Schulz, Lass-Hennemann, Sutterlin, Schächinger, & Vögele, 2013). Both physiological stress axes might be involved, as both cortisol (Maeda, Ogishima, & Shimada, 2019; Schulz, Strelzyk, et al., 2013) and beta-adrenergic activation (Eichler & Katkin, 1994; Herbert, Pollatos, Flor, Enck, & Schandry, 2010; Moor et al., 2005) may increase IAcc. It remains unclear, however, whether one of these axes was responsible for the increasing effect after a laboratory stressor (Schulz, Lass-Hennemann, et al., 2013). A limitation of one previous study was that only the peripheral branch of the SAM axis was activated (e.g., stimulation of beta1-adrenergic receptors by adrenaline and beta1-adrenergic blockade by esmolol infusion) (Moor et al., 2005), whereas the role of the central branch (e.g., central noradrenergic system) remained unclear. The first aim of the current study was, therefore, to elucidate the impact of an activation of the entire SAM axis by a pharmacological intervention on IAcc.

Central alpha2-adrenergic receptors have their highest density within the locus coeruleus (LC) (Coull, 1994) and the nucleus tractus solitarius (NTS) (Rockhold & Caldwell, 1980) and, as autoreceptors, mediate a negative feedback mechanism for central noradrenergic and sympathetic activity. Alpha2-antagonists have been shown to induce increased alertness, vigilance (Berridge & Foote, 1991) and sympathetic cardiovascular activation as indicated by increased heart rate (HR), systolic (SAP), and diastolic arterial blood pressure (DAP) (Philippsen et al., 2007). In summary, the blockade of alpha2-adrenergic receptors can be used to activate both central and peripheral components of the SAM axis.

Previous studies of *acute stress* on interoception have mainly investigated the role of normally functioning physiological stress axes of healthy individuals for IAcc. In contrast, the relationship between physiological stress axes and IAcc in *chronic stress* or *stress-related disorders*, such as MDD, remains unclear. Environmental stress and adverse life events, such as adverse childhood experiences (ACE), play an important role in the development and clinical course of MDD (Brown, Harris, & Hepworth, 1994; Brown, Schulberg, Madonia, Shear, & Houck, 1996; Kessler, 1997; Paykel, 2001). Therefore, it is not surprising that changes of stress hormones and neurotransmitter regulation related to the physiological stress axes have been associated with MDD. Noradrenaline has even been suggested to play a key role in the pathophysiology of MDD (Maletic, Eramo, Gwin, Offord, & Duffy, 2017). Especially regarding alpha2-adrenergic receptors, there is evidence suggesting increased affinity and density in the LC and the prefrontal cortex in MDD patients (Cottingham & Wang, 2012; Garcia-Sevilla et al., 1999; Ordway, Schenk, Stockmeier, May, & Klimek, 2003; Rivero et al., 2014). Interestingly, chronic social stress can affect alpha2-receptor regulation depending on receptor subtypes, timing, and brain region (Flugge, 1996, 1999; Flugge, van Kampen, Meyer, & Fuchs, 2003). ACE, especially as defined in this study as repeated physical or sexual abuse, constitute a severe chronic stress condition and an important risk factor for mental disorders including MDD. Furthermore, ACE affect the stress regulation systems (Heim, Ehlert, & Hellhammer, 2000; Orr, Metzger, & Pitman, 2002; Otte et al., 2016) and may therefore be one important reason for alterations in the stress systems in MDD (Heim et al., 2000; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Otte et al., 2005).

Thus, increased central alpha2-adrenergic receptor sensitivity characterized by enhanced affinity and density might be especially present in a subgroup of MDD patients with a history of ACE. Results of a study using a challenge test with an alpha2-receptor agonist in individuals with ACE but no MDD suggest increased alpha2 receptor sensitivity in association with childhood trauma (Lee, Fanning, & Coccaro, 2016). This highlights the necessity to disentangle potential effects of MDD and ACE on alpha2-adrenergic receptor function.

In summary, previous studies of *acute stress* effects on IAcc cannot reveal relevant processes underlying potential alterations of IAcc in *stress-related disorders*. The second aim of the current study was, therefore, to clarify the impact of an SAM axis activation on IAcc in healthy individuals with and without ACE, as well as in MDD patients with and without ACE.

We assessed MDD patients with and without ACE, and healthy individuals with and without ACE, with the aim of disentangling differential effects of MDD and ACE. Participants were tested once after intake of a yohimbine and once after intake of a placebo pill. Two indicators of interoception were measured in a common HCT: (a) IAcc, which is seen as most relevant indicator of interoception, and (b) IS, reflecting subjective beliefs about one's accuracy (Garfinkel et al., 2015). In accordance with previous studies of acute stress on IAcc (Schulz, Lass-Hennemann, et al., 2013), we hypothesized (I) an increase of IAcc and IS after yohimbine administration, but not after placebo intake. Furthermore, we expected (II) principally lower IAcc and IS in MDD and ACE groups than in healthy participants (Dunn et al., 2007; Terhaar et al., 2012). Finally, we expected (III) for yohimbine effects on cardiovascular activity and interoception to be stronger in individuals with potential upregulation of alpha2-adrenergic activity (MDD and ACE groups).

## Methods

### Participants

The study design was approved by the ethics committee of the German Society for Psychology (Deutsche Gesellschaft für Psychologie). All participants provided written informed consent. Healthy participants and outpatients received monetary reimbursement (100 €) for participation. Depressed patients and healthy participants were recruited by public postings and from our specialized affective disorder unit at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin.

Depressed patients were included if they fulfilled criteria for a current episode of MDD as assessed by a trained psychologist (L.K.K. or C.E.D.) using a German version of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) axis I (SCID-I) (Wittchen, Zaudig, & Fydrich, 1997) to validate psychiatric diagnoses. In addition to the SCID-I interview, current depressive symptoms were assessed using a clinical rating scale and a questionnaire (Montgomery Asberg Depression Rating Scale [MADRS] (Montgomery & Asberg, 1979; Williams & Kobak, 2008) and the Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996).

ACE was defined as repeated physical or sexual abuse at least once a month over one year or more (Heim et al., 2000) before the age of 18. Results by Heim et al. (2000) suggest long-lasting hyperreactivity of the autonomic nervous system after the

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experience of ACE. ACE was assessed by a screening interview and validated by the German version of the semistructured interview, the Early Trauma Inventory (ETI) (Bremner, Vermetten, & Mazure, 2000; Wingenfeld et al., 2011). In addition, adverse childhood experiences were measured using a German version of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Wingenfeld et al., 2010).

For the MDD groups, exclusion criteria were schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, dementia, abuse of alcohol or drugs, and panic disorder. Healthy participants with and without ACE were free of any current mental disorder. Further exclusion criteria for all participants were central nervous system (CNS)-relevant diseases, neurological diseases, severe physical conditions, for example diabetes Type 1 and 2, steroid diseases, hypertension, current infections, pregnancy, and the intake of psychotropic medication. Physical health criteria were checked by physical examination, clinical interview, and blood count.

Of 138 participants, data of 24 participants were excluded from analysis because participants completed only one testing day or data were incomplete due to technical malfunction or insufficient data quality. The final dataset consisted of 114 participants: 22 MDD patients with ACE (MDD+/ACE+), 24 MDD patients without ACE (MDD+/ACE−), 23 participants with ACE but no current or lifetime MDD (MDD−/ACE+), and 45 participants with no current or lifetime MDD and no childhood adversity (MDD−/ACE−).

### Assessment of cardiovascular activity

Electrocardiogram (ECG) data were assessed using a Biopac MP150 amplifier system at 1 kHz sampling rate and a hardware high-pass filter of 0.5 Hz. Discrete blood pressure measurements were taken using a standard, automated pressure cuff, which was fixed around the right upper arm (Dinamap 1846 SX). ECG data of 5 min resting periods were analyzed with WinCPRS 1.160 software. Beat-to-beat HR data were calculated from semiautomatic QRS detection.

### Interoceptive task

Due to the repeated measurement design of the study, we assessed IAcc based on the HCT only, as previous studies suggest that IAcc in the HCT task was increased if participants had completed a heartbeat discrimination task (HDT), an alternative method to assess cardiac IAcc, before (Phillips, Jones, Rieger, & Snell, 1999; Schaefer, Egloff, & Witthoft, 2012). We presented four silent intervals (25, 35, 45, and 55 s) in random order. One training trial of 25 s length preceded the three experimental trials. Participants were asked to focus their attention on and to count their heartbeats without taking their pulse during each of these periods (and to indicate zero if they have not counted any), with a tone signaling their beginning and end. Participants were continuously monitored during assessment to ensure that they followed all study instructions. IAcc was calculated using the formula:

$$\mathrm{IAcc_{HCT}} = \frac{1}{4}\sum_{k=1}^{4}\left(1 - \frac{\left(\left|\begin{array}{l}\text{no. of recorded heartbeat } s_k - \\ \text{no. of perceived heartbeat } s_k\end{array}\right|\right)}{\text{no. of recorded heartbeat } s_k}\right)$$

The majority of healthy individuals underestimate the number of heartbeats in the HCT (Zamariola, Maurage, Luminet, & Corneille, 2018), whereas within individuals with panic disorder, there is a certain proportion of people who overestimate the number of perceived heartbeats (Willem Van der Does, Antony, Ehlers, & Barsky, 2000). To test for potential over- or underreporting biases of heartbeats, we calculated an alternative formula without absolute values, as previously introduced (Rost, Van Ryckeghem, Schulz, Crombez, & Vögele, 2017):

$$\mathrm{IAcc_{bias}} = \frac{1}{4}\sum_{k=1}^{4}\left(\frac{\left(\begin{array}{l}\text{no. of perceived heartbeat } s_k - \\ \text{no. of recorded heartbeat } s_k\end{array}\right)}{\text{no. of recorded heartbeat } s_k}\right)$$

After each trial, participants were asked to indicate the number of perceived heartbeats and subsequently asked to rate their confidence on how correct they were on a scale ranging from 0 (*not sure at all*) to 8 (*absolutely sure*) as indicator of IS.

### Pharmacological intervention

On one testing day, participants received 10 mg of oral yohimbine (Spiegel, DESMA), whereas on the other testing day they received a placebo (P-Pills, Lichtenstein). In previous studies, yohimbine dosages of 5 mg 20 mg have been shown to affect cognitive processes (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999; Soeter & Kindt, 2011, 2012; Wingenfeld et al., 2013).Lower dosages minimize the risk of adverse side effects. Order of drug administration was counterbalanced across participants, and drugs were administered in a double-blinded (to experimenter and participants) fashion.

### Procedure

Psychological assessment took place on a separate day prior to the laboratory testing. Participants were tested in two separate laboratory sessions. At least one day elapsed between testing sessions, with an average interval between both sessions of 5 days (5.4, *SD*: 5.2). The experimental setup was identical on both days, except for the administration of either yohimbine or placebo. All participants were requested to refrain from physical activity and caffeine consumption on the testing days. Upon arrival at the laboratory at 09:30 h, participants were seated in a comfortable chair and underwent a first baseline ECG assessment (5 min) and discrete blood pressure measurement after a 5-minute resting period. Thereafter participants received orally either yohimbine or placebo (09:45 h), followed by a 60-minute waiting period (until 10:45 h) to allow the drug to cross the gastric passage. The HCT was part of an extended study setup, the results of which will be and has been reported elsewhere (De Punder et al., 2018; Deuter et al., 2020; Kuehl et al., 2020). The main outcome paradigms included different cognitive paradigms in a fixed order (total duration of 60 min including breaks). As plasma peak levels of yohimbine occur approx. 90 min after oral intake (O'Carroll et al., 1999; Peskind et al., 1995), it is plausible that after a delay of approx. 135 min between intake and HCT, drug effects are still persisting. Prior to the HCT, ECG (5 min) and blood pressure were monitored again (11:45 h). The timeline of the experiment is presented in Figure 1. The total duration of the experimental protocol was approx. 2½ hr.

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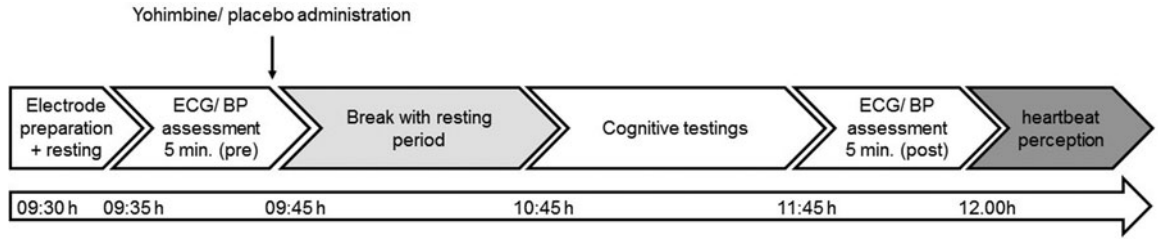


**Figure 1.** Timeline of experimental setup. Procedures were identical on both testing days, except for the administration of either yohimbine or a placebo substance.

### *Statistical analysis*

Demographic and clinical characteristics, including depression and childhood trauma scores in all subscales of the BDI-II, the MADRS, the CTQ, and the ETI, were analyzed with one-way analysis of variance (ANOVA) for continuous variables or $\chi^2$ test for dichotomous variables across the four groups (MDD −/ACE−, MDD−/ACE+, MDD+/ACE−, MDD+/ACE+). If applicable, post-hoc group differences were evaluated with Tukey HSD tests. Cardiovascular data (HR, SAP, DAP) were evaluated using a $4 \times 2 \times 2$ mixed-design ANOVA with the between-subjects factor "group," and the within-subjects factors "drug" (yohimbine, placebo) and "time" (pre, post). Furthermore, a $4 \times 2$ mixed-design ANOVA with the between-subjects factor "group" and the within-subjects factor "drug" was used to evaluate effects on the dependent variables $IAcc_{HCT}$, $IAcc_{bias}$, and IS. Post-hoc tests of significant ANOVA effects were carried out using *T*-tests for dependent samples. To elucidate the determinants of $IAcc_{HCT}$ and $IAcc_{bias}$, we calculated linear multiple regression models (enter method), one for each drug condition (Model 1: placebo, Model 2: yohimbine), separately for the criteria $IAcc_{HCT}$ and $IAcc_{bias}$. Predictors of $IAcc_{HCT}$ and $IAcc_{bias}$ were HR, SAP, DAP (at the respective measurement occasion), depression score (BDI-II), childhood trauma score (CTQ), and IS. Critical alpha-level was set to .05 in all analyses. Analyses were carried out using SPSS version 24 (IBM Corp.).

## Results

### *Sample characteristics*

There were no significant differences between groups regarding sex, age, and body mass index (BMI), although the comparison of age and BMI across groups reached trend level, mainly caused by higher values in the MDD+/ACE+ group.

As expected, the two MDD groups (MDD+/ACE−, MDD +/ACE+) showed significantly higher total scores on the MADRS and BDI than the two healthy groups (MDD−/ACE−, MDD−/ACE+), whereas neither the two MDD groups, nor the two healthy groups differed from each other in depression scores. In addition to the diagnosis of a current MDD, 13 patients fulfilled the criteria for one or more mental comorbid disorders (MDD+/ACE− [$n = 6$]: four with social phobia, one somatoform pain disorder, and one avoidant personality disorder; MDD +/ACE+: [$n = 7$]: three with phobia [two social], one with somatoform pain disorder, one with bulimia nervosa, four with posttraumatic stress disorder [PTSD, related to ACE], and one mixed personality disorder).

In line with our recruitment criteria, the ETI total score and the CTQ total score clearly differentiated between groups with and without ACE, in that ETI total scores were higher in the MDD+/ACE+ and the MDD−/ACE+ groups compared to the MDD+/ACE− and MDD−/ACE− groups. There were no differences within groups with ACE and groups without ACE. For the CTQ total score, significant differences between all groups were observed, with lowest scores in the MDD−/ACE− group, followed by the MDD+/ACE− group, the MDD−/ACE+, and the MDD+/ACE+ group (in ascending order).

Group differences, ANOVA statistics and post-hoc comparisons with regard to depression scores and childhood trauma questionnaires are presented in Table 1.

### *Cardiovascular data*

#### *Systolic arterial blood pressure (SAP)*

A significant Drug × Time interaction ($F[1,105] = 49.69$; $p < .001$; $\eta_p^2 = .32$) indicated a stronger SAP increase from "pre" to "post" in the yohimbine ($p < .001$; $d = 1.08$) than in the placebo condition. Post-hoc analyses revealed, however, that SAP increased from "pre" to "post" also in the placebo condition, but to a lesser extent ($p < .01$; $d = .26$). Neither mean SAP, nor SAP reactivity ("pre" vs. "post") to yohimbine differed between groups. Cardiovascular data are presented in Table 2.

#### *Diastolic arterial blood pressure (DAP)*

Comparable to SAP, we observed a significant Drug × Time interaction ($F[1,105] = 16.00$; $p < .001$; $\eta_p^2 = .13$). Post-hoc analyses showed that DAP increased from "pre" to "post" after placebo and yohimbine intake, but more in the yohimbine ($p < .001$; $d = 1.01$) than in the placebo condition ($p < .01$; $d = .27$). Moreover, a significant Group × Time interaction ($F[3,105] = 3.77$; $p = .013$; $\eta_p^2 = .10$) suggests higher DAP at measurement "post" than at "pre" in the MDD−/ACE− ($d = 1.05$), the MDD −/ACE+ ($d = .77$) and the MDD+/ACE− groups ($d = .89$; all *p*s $< .001$), but not in the MDD+/ACE+ group ($p > .10$). Neither mean DAP, nor DAP reactivity ("pre" vs. "post") to yohimbine differed between groups.

#### *Heart rate (HR)*

Mean HR was significantly higher in the MDD+/ACE− group (76.6 [2.2] bpm) than in the MDD−/ACE− group (68.03 [1.5] bpm; $p = .001$), whereas the other groups did not differ from each other (MDD−/ACE+: 71.6 [2.2] bpm; MDD+/ACE+: 72.2 [2.3] bpm; $F[3,105] = 3.65$; $p = .015$; $\eta_p^2 = .09$). Furthermore, we found a significant Drug × Time interaction ($F[1,105] = 11.06$; $p = .001$; $\eta_p^2 = .10$). Post-hoc analyses showed that HR decreased from "pre" to "post" in both "drug" conditions (yohimbine: $d = -.97$; placebo: $d = -1.16$; all *p*s $< .001$), but the decrease was more marked after placebo than after yohimbine intake. HR reactivity to yohimbine did not differ between groups.

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**Table 1.** Sample characteristics with regard to demographics, depression and childhood adversity

| | | MDD−/ACE− | | MDD−/ACE+ | | MDD+/ACE− | | MDD+/ACE+ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* = 45 | | *n* = 23 | | *n* = 24 | | *n* = 22 | | | | | |
| Measure | unit | *M* | (*SD*) | *M* | (*SD*) | *M* | (*SD*) | *M* | (*SD*) | $F/\chi^2$ | *Df* | *p* | Post-hoc difference (Tukey HSD) |
| Sex | m/f | 23/22 | | 13/10 | | 13/11 | | 9/13 | | 1.27 | 3 | .74 | |
| Age | years | 35.4 | (10.5) | 33.8 | (10.7) | 33.8 | (10.6) | 41.3 | (11.3) | 2.54 | 3,113 | .06 | |
| BMI | $kg/m^2$ | 23.3 | (3.3) | 23.8 | (3.1) | 22.7 | (3.4) | 25.2 | (2.9) | 2.52 | 3,113 | .06 | |
| *Depression* | | | | | | | | | | | | | |
| MADRS total score | | 0.7 | (1.2) | 1.6 | (1.7) | 28.9 | (5.4) | 28.1 | (8.2) | 339.68 | 3,113 | <.001 | 1, 2 < 3, 4 |
| BDI total score | | 1.6 | (1.9) | 4.7 | (4.7) | 24.4 | (6.6) | 26.1 | (9.1) | 152.75 | 3,113 | <.001 | 1, 2 < 3, 4 |
| *Adverse childhood experiences* | | | | | | | | | | | | | |
| ETI total score | | 16.4 | (22.6) | 523.6 | (342.4) | 140.9 | (209.7) | 724.0 | (465.4) | 41.75 | 3,113 | <.001 | 1, 3 < 2, 4 |
| CTQ total score | | 30.6 | (6.0) | 57.2 | (14.0) | 40.0 | (10.5) | 68.0 | (18.8) | 57.38 | 3,113 | <.001 | 1 < 3 < 2 < 4 |

MDD = major depressive disorder, ACE = adverse childhood experiences, BMI = body mass index, MADRS = Montgomery Asberg Depression Rating Scale, BDI = Becks Depression Index, ETI = Early Trauma Interview, CTQ = childhood trauma questionnaire, M = mean, *SD* = standard deviation.

## Interoception

### Interoceptive accuracy (IAcc)

We observed a significant main effect of "drug" ($F[1,110] = 5.60$; $p = .02$; $\eta_p^2 = .05$), which was explained by a significant Group × Drug interaction ($F[1,110] = 2.82$; $p = .042$; $\eta_p^2 = .07$), indicating lower $IAcc_{HCT}$ after yohimbine than after placebo administration in the group MDD−/ACE+ ($p = .001$). There were neither differences in $IAcc_{HCT}$ between "drug" conditions in any other group (see Figure 2a) nor differences between groups. There were statistical trends suggesting difference in age and BMI between groups (mainly due to descriptively higher age and BMI in the MDD +/ACE+ group compared to the MDD+/ACE− group). As age (Khalsa, Rudrauf, & Tranel, 2009) and BMI (Herbert, Blechert, Hautzinger, Matthias, & Herbert, 2013; Herbert & Pollatos, 2014) may potentially affect IAcc, we included "age" and "BMI" as covariates in the statistical model in a follow-up analysis. After controlling for both variables, the Group × Drug interaction remained significant ($F[3,108] = 2.85$; $p = .041$; $\eta_p^2 = .07$). When evaluating $IAcc_{bias}$, there were neither significant group differences, nor any yohimbine effects (Figure 2b).

### Interoceptive sensibility (IS)

There were no significant differences between groups or between "drug" conditions (see Figure 3).

### Regression analyses

$IAcc_{HCT}$ after placebo (Model 1) was significantly predicted by HR, SAP, DAP, BDI (measuring depression), and CTQ (measuring childhood trauma) scores and IS as indicated by a statistical significance of the overall model (see Table 3). Among all predictors, however, only HR and IS remained as a significant predictor. After yohimbine (Model 2), the overall model to predict $IAcc_{HCT}$ was significant (Tab. 3). In this model, significant predictors were depression scores, childhood trauma scores, and IS among all predictors. With regard to the criterion $IAcc_{bias}$, neither the overall Models 1 and 2, nor any of the single predictors reached significance level.

## Discussion

The current study examined the effect of SAM axis activation by the alpha2-adrenergic antagonist yohimbine versus placebo on IAcc and IS. We investigated two healthy groups with and without ACE and two MDD groups with and without ACE, as both, MDD and ACE, may be associated with an upregulation of central alpha2-adrenoceptors. All patients and participants were free of antidepressant or cardiovascular medication. An increase of SAP and DAP, and a smaller decrease in HR in the yohimbine compared to the placebo condition suggests effective stimulation of the SAM axis by alpha2-adrenoceptor blockade. In contrast to our expectations (Hypotheses I and III), however, we observed reduced $IAcc_{HCT}$ after yohimbine intake in the MDD−/ACE+, but not in any of the other groups. Age and BMI did not affect these results. To test if these effects were due to a selective over- or underreporting bias (Zamariola et al., 2018), and, therefore, the cognitive strategy to perform the HCT (Desmedt, Luminet, & Corneille, 2018), we also evaluated the bio-polar index $IAcc_{bias}$ which indicates positive values in overreporting and negative values in underreporting (Rost et al., 2017). As $IAcc_{bias}$ did not differ between groups and did not respond to yohimbine administration, it is unlikely that the effect of yohimbine on $IAcc_{HCT}$ is solely due to an over- or underreporting bias. In contrast to $IAcc_{HCT}$, IS did not respond to yohimbine intake in any group. This finding suggests that the yohimbine effects on interoception are specific for the actual perception of heartbeats, whereas this (potentially temporary) effect does not translate into a dispositional tendency to be internally self-focused (Garfinkel et al., 2015).

After placebo administration, HR was identified as a negative and IS as a positive predictor of $IAcc_{HCT}$, which is in line with the multifaceted model of interoception by Garfinkel et al. (2015)

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**Table 2.** Indicators of cardiovascular activity before and after the intake of yohimbine and a placebo substance

| | | | | MDD−/ACE− | | MDD−/ACE+ | | MDD+/ACE− | | MDD+/ACE+ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *n* = 45 | | *n* = 23 | | *n* = 24 | | *n* = 22 | |
| Measure | Unit | Drug | Measurement occasion | *M* | (*SEM*) | *M* | (*SEM*) | *M* | (*SEM*) | *M* | (*SEM*) |
| SAP[a] | mmHg | Yohimbine | Pre | 114.2 | (1.9) | 113.4 | (2.7) | 113.3 | (2.7) | 121.0 | (2.8) |
| | | | Post[b] | 126.9 | (2.3) | 126.0 | (3.4) | 123.2 | (3.3) | 131.3 | (3.5) |
| | | Placebo | Pre | 115.3 | (2.0) | 114.0 | (2.8) | 114.6 | (2.8) | 116.8 | (3.0) |
| | | | Post[c] | 117.3 | (1.9) | 118.6 | (2.7) | 116.1 | (2.7) | 119.0 | (2.8) |
| DAP[a] | mmHg | Yohimbine | Pre | 66.6 | (1.2) | 68.1 | (1.8) | 67.5 | (1.8) | 71.4 | (1.8) |
| | | | Post[b] | 74.6 | (1.4) | 75.6 | (2.0) | 75.0 | (2.0) | 73.0 | (2.1) |
| | | Placebo | Pre | 66.9 | (1.7) | 69.4 | (2.4) | 67.1 | (2.4) | 71.6 | (2.6) |
| | | | Post[c] | 68.9 | (1.4) | 72.1 | (2.0) | 71.6 | (2.0) | 71.7 | (2.1) |
| HR[a] | bpm | Yohimbine | Pre | 71.6 | (1.9) | 74.3 | (2.8) | 80.9 | (2.8) | 74.7 | (2.9) |
| | | | Post[b] | 64.6 | (1.6) | 67.6 | (2.3) | 73.7 | (2.3) | 68.8 | (2.5) |
| | | Placebo | Pre | 72.3 | (1.7) | 77.2 | (2.4) | 80.9 | (2.4) | 77.0 | (2.5) |
| | | | Post[b] | 63.5 | (1.4) | 67.1 | (2.0) | 71.1 | (2.0) | 68.2 | (2.1) |

[a]SAP = systolic arterial pressure, DAP = diastolic arterial pressure, HR = heart rate, M = mean, SEM = standard error mean.
[b]Differences between "pre" and "post" significant at $p < .001$ (averaged over all groups).
[c]Differences between "pre" and "post" significant at $p < .01$.

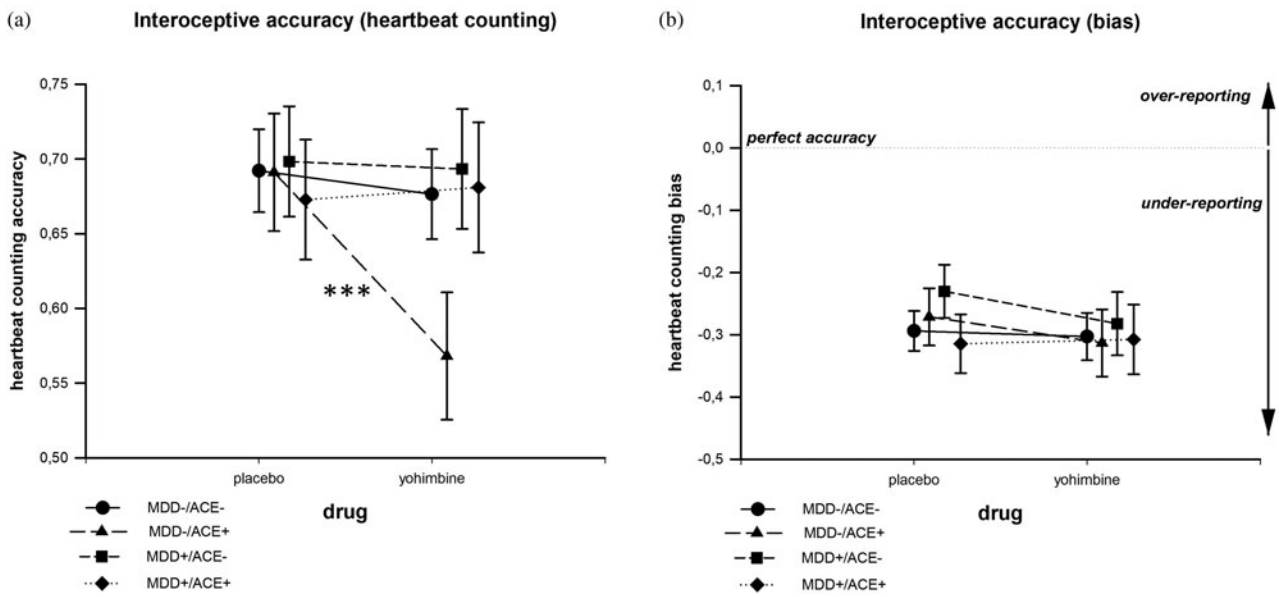


**Figure 2.** Interoceptive accuracy (IAcc) in the heartbeat counting task after the intake of yohimbine and a placebo substance. In the MDD−/ACE+ group, IAcc was lower after yohimbine than after placebo intake (a). When evaluating the over- versus underreporting bias of IAcc, no group difference or drug effect emerged (b).

and extended by Forkmann et al. (2016). In this model, cardiovascular activation (i.e., HR) and IS are deemed proximate levels of $IAcc_{HCT}$ that may interact in both bottom-up and tow-down regulatory circuits (Forkmann et al., 2016; Garfinkel et al., 2015). Therefore, the relationship of IAcc with HR and IS can be seen as support for the validity of our findings. In contrast, after yohimbine administration, depression and childhood trauma scores were identified as positive (depression) and negative (childhood trauma) predictors of $IAcc_{HCT}$, whereas HR was not significant. First, we conclude that alpha2-adrenoceptors play a role in mediating interoceptive signal processing. Second, we conclude that noradrenergic activation can decrease interoceptive accuracy in healthy individuals with ACE which is supported by Drug × Group interaction effect and the results of the regression analysis identifying the CTQ score as a negative predictor of $IAcc_{HCT}$. This speaks in favor of the hypothesis that upregulated alpha2-adrenoreceptors are associated with ACE. In contrast, we did not find such effects regarding MDD so that our results do not support the hypothesis

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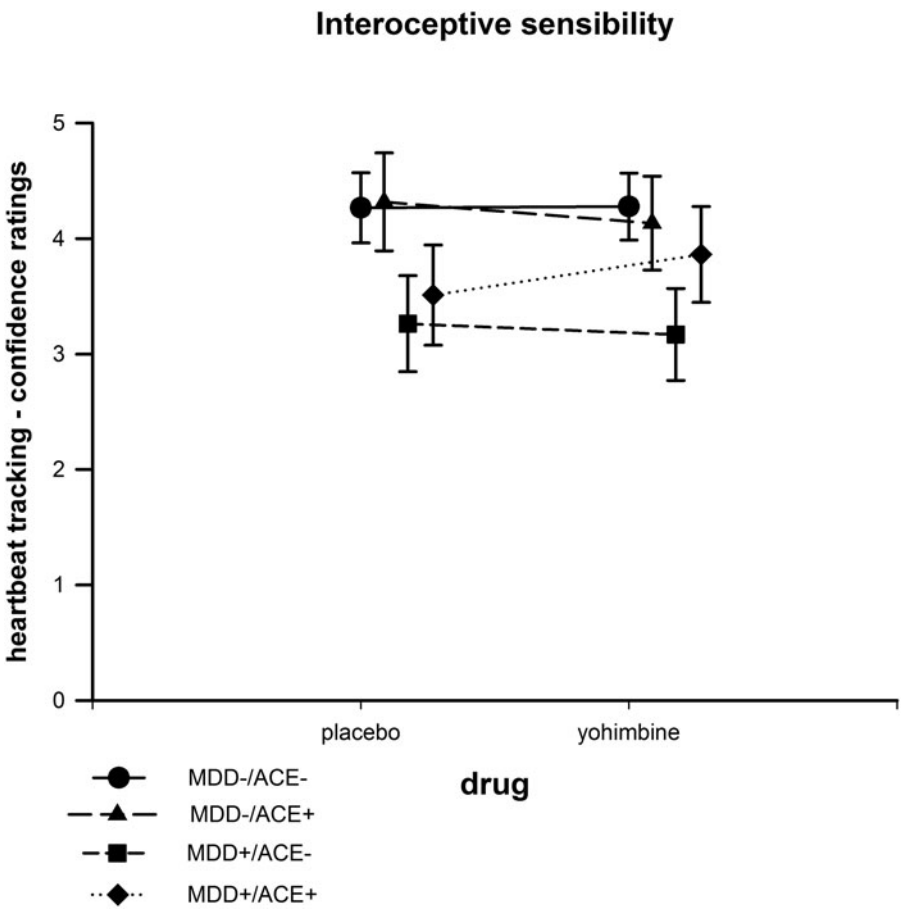


**Figure 3.** Interoceptive sensibility based on confidence ratings in the heartbeat counting task after the intake of yohimbine and a placebo substance.

of upregulated alpha2-adrenoreceptors in MDD. Finally, the finding that neither IS, nor any indicator of cardiovascular activation was a predictor of $IAcc_{bias}$ suggests that cognitive biases of over- or underreporting are unrelated to the actual strength of body signals and subjective confidence about one's accuracy to report those signals.

Two important structures of the central noradrenergic system show a particularly high concentration of alpha2-adrenergic receptors: the LC and the NTS (Coull, 1994; Rockhold & Caldwell, 1980). The LC is involved in mediating alpha2-adrenergic effects on alertness, vigilance, and attention (Aston-Jones, Rajkowski, & Cohen, 1999; Berridge & Foote, 1991; Coull, Nobre, & Frith, 2001; Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999), whereas alpha2-adrenergic effects on the NTS are responsible for cardiovascular sympathetic activation, such as an increase in HR, SAP, and DAP (Grossman, Rea, Hoffman, & Goldstein, 1991; Philippsen et al., 2007). Furthermore, alpha2-adrenoreceptors mediate the processing and integration of visceral–afferent signals in the arterial baroreflex circuitries (Hayward, Riley, & Felder, 2002; Kubo, Goshima, Hata, & Misu, 1990; Sved, Tsukamoto, & Schreihofer, 1992; Yamazaki & Ninomiya, 1993).

For interoception, at least two processes of an SAM axis activation by yohimbine may be of relevance: the alertness component of attention and sympathetic activation. Both processes, however, can impact interoception in opposite ways if affected by alpha2-adrenergic blockade. On the one hand, peripheral sympathetic activation increases cardiac contractility (Scherhag, Stastny, Pfleger, Voelker, & Heene, 1999), which increases IAcc (Eichler & Katkin, 1994; Herbert et al., 2010; Moor et al., 2005; Schandry, Bestler, & Montoya, 1993). On the other hand, alpha2-antagonists facilitate alertness, but reduce capacity for focused and selective attention (Clark, Geffen, & Geffen, 1986, 1987; Hermans et al., 2011). The dose used in the current study (10 mg) may have resulted in a predominance of the reducing effect on focused attention over an increase in sympathetic activity (at least in the MDD−/ACE+ group). Decreased IAcc in SAM axis activation may be part of an adaptive response in healthy participants with ACE. Acute stress could, therefore, result in suppression or denial of physical symptoms as survival and coping mechanism (Bernstein & Claypool, 2012; Schaan et al., 2019) and thus promote resilience in this group.

A change of $IAcc_{HCT}$ in response to the relatively low dose of 10 mg yohimbine in the current study suggests that an upregulation of alpha2-adrenergic receptors, such as to be expected after ACE, is necessary to result in altered $IAcc_{HCT}$. In the other groups, this dose may not have been sufficient to affect IAcc, as they probably do not show an upregulated sensitivity of alpha2-adrenergic receptors. Taken together with a recent study using an alpha2-receptor agonist challenge test in individuals with ACE (Lee et al., 2016), the present results support the notion of increased sensitivity of central alpha2-adrenergic receptors associated with ACE.

Afferent parasympathetic visceral–afferent signals are relayed over the cranial nerves (VII, IX, X) and the NTS, whereas sympathetic visceral–afferent signals are transmitted via the lamina1 layer of the spinal dorsal horn, before thalamic nuclei, the anterior cingulate, and insular cortices are reached (Cameron, 2001; Craig, 2002; Schulz, 2016). While the sympathetic pathway includes the LC (Cameron, 2001), some sympathetic information is relayed via

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**Table 3.** Predictors of interoceptive accuracy after placebo (regression Model 1) and yohimbine administration (regression Model 2)

| Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|
| Criterion: IAcc[a] after placebo intake | | | | Criterion: IAcc[a] after yohimbine intake | | | |
| *df* | *F* | *p* | $R^2$ | *df* | *F* | *P* | $R^2$ |
| **6, 108** | **2.20** | **.049** | **.11** | **6, 108** | **3.22** | **.006** | **.15** |
| Predictors | B | *T* | *p* | Predictors | B | *T* | *P* |
| Constant term | | 4.937 | | Constant term | | 4.877 | |
| **HR[b]** | **−.244** | **−2.536** | **.013** | HR[b] | −.153 | −1.683 | .095 |
| SAP[c] | .100 | .763 | .447 | SAP[c] | −.008 | −.074 | .941 |
| DAP[d] | −.098 | −.740 | .461 | DAP[d] | −.082 | −.746 | .457 |
| BDI-II[e] Total score | .145 | 1.394 | .166 | **BDI-II[e] Total score** | **.264** | **2.582** | **.011** |
| CTQ[f] Total score | −.074 | −.732 | .466 | **CTQ[f] Total score** | **−.253** | **−2.579** | **.011** |
| **IS[g]** | **.239** | **2.527** | **.013** | **IS[g]** | **.269** | **2.903** | **.004** |

*Note*: Significant predictors in bold. [a]interoceptive accuracy; [b]heart rate; [c]systolic arterial blood pressure; [d]diastolic arterial blood pressure; [e]Beck's Depression Inventory II; [f]Childhood Trauma Questionnaire; [g]interoceptive sensibility.

the NTS (Craig, 2002), which may particularly include (alpha2-) adrenergic receptor circuitries. Both neural pathways are considered relevant for mediating visceral–afferent neural signals associated with heartbeat perception (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Pollatos, Schandry, Auer, & Kaufmann, 2007). On the one hand, transcutaneous vagal nerve stimulation increases of IAcc (Villani, Tsakiris, & Azevedo, 2019), which implies that the parasympathetic pathway is essential for cardiac interoception. On the other hand, a blockade of the alpha2-adrenergic receptor circuits in individuals with a potentially high receptor density or sensitivity decreases IAcc, suggesting that the sympathetic (neural) pathway is similarly important. One may conclude, therefore, that under homeostatic conditions, neural signal transmission from both pathways is crucial for an adequate interoception, whereas an acute or chronic allostatic condition may disrupt one or both pathways, potentially contributing to lower IAcc.

Lower IAcc has been previously reported in a moderately depressed community sample compared to healthy individuals (Dunn et al., 2007), and reduced cortical representation of interoceptive signals in MDD (Terhaar et al., 2012). In contrast to Hypothesis II, in the current study, there were no differences between MDD patients and healthy participants, although the present sample size was larger than in both previous studies. The inclusion of MDD patients without antidepressant medication in the current study allowed us to disentangle possible effects associated with MDD-specific psychobiological alterations (e.g., increased central alpha2-adrenergic receptor sensitivity) from pharmacodynamic effects of antidepressive medication including their impact on cardiovascular activity (Glassman, 1998), physiological stress axes activity (Surget et al., 2011), and attention (Constant et al., 2005), which may all affect interoception. As in both earlier studies a substantial proportion of MDD patients were taking antidepressants (mainly selective serotonin reuptake inhibitors, SRIs) (Dunn et al., 2007; Terhaar et al., 2012), it cannot be ruled out that the previously reported group differences in interoception may be due to pharmacological effects of medication.

We assessed ACE with two different measures: a semistructured interview (ETI) and a self-reporting questionnaire (CTQ). Group allocation was based on the ETI. However, in contrast to the ETI, which did not show higher scores individuals with MDD only, the CTQ also reflected an association with MDD diagnosis. Participants with MDD had higher CTQ scores compared to healthy controls, and this was true for both participants with and without ACE. Such a discrepancy between questionnaires and interview measures has been described in previous studies (e.g., Cisler et al., 2013) and can be attributed to the survey methodology. The direction of causality of this effect of MDD on CTQ scores remains unknown. It is of course plausible that MDD individuals have had more negative experiences in childhood than healthy controls, even if these are not severe enough to meet the ACE inclusion criteria. Again, within the ACE+ groups, the more severely affected may also show greater vulnerability to MDD. Nevertheless, the ETI can be considered the more sensitive measure compared to questionnaires (Baldwin, Reuben, Newbury, & Danese, 2019); and the ETI does not show these differences. An alternative explanation would, therefore, be a reporting bias in the questionnaire, which leaves no room for questions and assessments by the investigator. MDD patients might have retrospectively assessed their childhood more negatively (Colman et al., 2016).

### Limitations

Since we tested only patients without antidepressive medication, we cannot make any claim about how the intake of medication might affect our findings. Thus, the current findings of "normal" IAcc (placebo condition) in MDD may have to be interpreted with caution due to the limited representativeness for those MDD patients who receive antidepressant medication. We assessed IAcc only after drug intake, whereas no baseline assessment took place to reduce the possible impact of learning, as $IAcc_{HCT}$ is subject to moderate training effects (Wittkamp, Bertsch, Vogele, & Schulz, 2018). Although the repeated-measurement design provided a within-subjects control condition, this baseline assessment would have allowed controlling for occasion-specific variance. Furthermore, IAcc was only assessed with the HCT, although the additional use of the HDT would have provided more insights on attentional processes. We

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decided to present only the HCT to overcome potential sequence effects if the HDT is presented before the HCT (Phillips et al., 1999; Schaefer et al., 2012). On the one hand, recent methodological studies suggested that IAcc assessed by the HCT is potentially correlated with knowledge of one's heart rate (Murphy et al., 2018) or susceptibility to cognitive strategies (Desmedt et al., 2018). On the other hand, a substantial overlap with heartbeat-evoked potentials as neurophysiological indicator of cardiac interoception (Mai, Wong, Georgiou, & Pollatos, 2018; Pollatos & Schandry, 2004; Yuan, Yan, Xu, Han, & Yan, 2007) and reduced $IAcc_{HCT}$ in individuals with a degeneration of afferent autonomic nerves (Pauli, Hartl, Marquardt, Stalmann, & Strian, 1991) support the validity of this task in terms of its underlying neurophysiology. One could conclude, therefore, that although $IAcc_{HCT}$ may also be affected by potential confounding variables, it represents a well-validated method to reflect the processing of afferent signals from the cardiovascular system. Furthermore, an intravenous administration of yohimbine would have allowed a more precise timing of pharmacological effects, however, we decided for a less invasive way of yohimbine administration to avoid interference with the physiological stress axes. Finally, in the current study we focused on SAM axis activity as outcome measure, because alpha2-adrenergic receptors are seen as one component of this axis. Nevertheless, it needs to be acknowledged that activity of the HPA axis may also be affected by SAM axis activity. Potential interaction effects of both stress axes, however, as well as the role of other stress-associated mechanisms for IAcc, such as immune system activity (Khalsa et al., 2018; Savitz & Harrison, 2018), remain to be addressed in future studies. Follow-up studies may also wish to investigate if negative findings in the MDD+/ACE+ group may be due to a specific dysregulation of HPA axis activity in MDD patients such as blunted HPA axis responses to acute stress in a subset of patients (Burke, Davis, Otte, & Mohr, 2005; Gold, 2015; Gold & Chrousos, 2002). In addition, the current sample size did not allow for further analyses of effects of timing and duration of ACE. As long-lasting effects of ACE are probably related to sensitive phases in development (e.g., for review: Lupien, McEwen, Gunnar, & Heim, 2009), this aspect should also be addressed in future studies.

### Conclusions

The present study shows effective activation of the SAM axis in healthy individuals with and without ACE as well as in MDD patients with and without ACE after intake of 10 mg of the alpha2-adrenergic antagonist yohimbine, as indicated by HR, SAP, and DAP levels. Only in the healthy group with ACE yohimbine intake resulted in reduced $IAcc_{HCT}$, which may be explained by extenuated focused attention associated with central noradrenergic activation. The underlying process may involve a persisting upregulation of alpha2-adrenoreceptors in the LC and/or suppression of physical symptoms in acute stress after ACE.

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