# Individual differences in dopamine-related traits influence mood effects of dopamine D2-antagonist and antidepressant treatment expectations

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## Abstract

**Background:** High trait anhedonia and low trait extraversion have both been previously related to not only low state positive affect but also depressive disorders, disrupted reward processing, and altered mesolimbic dopaminergic signaling. Research on placebo responses suggests that treatment expectations may alter dopamine signaling, elevate positive affect, and reduce depressive symptoms in anhedonic individuals. However, it remains unclear whether such antidepressant placebo responses depend on putative low baseline dopaminergic functioning in high anhedonia and low extraversion. The present study investigates how interindividual differences in these traits influence positive affective responses under manipulation of dopamine and treatment expectations.

**Materials and Methods:** In a randomized, double-blind 2×2 design ($N$ = 297), we administered either placebo or the dopamine D2 receptor antagonist sulpiride (400 mg), and manipulated treatment expectations by telling participants that they received either a mood-elevating drug or an inactive substance. Moreover, we assessed trait anhedonia and extraversion, and had participants rate their state positive affect at 6 different time points before and after treatment.

**Results:** Trait anhedonia and extraversion, as well as a broad trait positive affectivity factor, predicted state positive affect across time points. Importantly, effects of sulpiride and antidepressant treatment expectations on positive affect were moderated by dopaminergic traits such that sulpiride increased state positive affect in high anhedonia but decreased it in low

anhedonia. Similarly, antidepressant treatment expectations raised positive affect in low extraversion but reduced it in high extraversion.

**Conclusions:** This study demonstrates that dopamine-related individual differences moderate the effects of both sulpiride and a placebo intervention on positive affective state.

Keywords: Anhedonia, dopamine, depressive disorders, treatment expectations, positive affect

## Significance Statement

In one of the first pharmacological studies examining the effects of treatment expectations and dopamine on mood in a large, healthy sample, we observed that lower baseline positive affectivity was linked to stronger mood-elevating treatment responses to both a placebo and a dopamine-related drug over time. This highlights how individual differences in relevant traits can influence treatment effectiveness, offering valuable insights for tailoring personalized approaches to depression care.

## Introduction

Human beings vary in their capacity to experience positive affect. Among healthy individuals, this variability is reflected across the expressiveness of traits like anhedonia,[1,2] extraversion[3,4] or broader dimensions of positive affectivity.[5] Apart from being a trait with varying levels in the general population, low positive affect—or anhedonia—represents a cardinal symptom of depressive disorders, which rank among the most burdensome and disabling conditions globally.[6,7]

Individual differences in anhedonia,[8] depression,[9] and extraversion[10,11] are presumably related to variations in dopaminergic functioning. Anhedonia reflects impaired motivation and reward processing, both of which are closely tied to dopamine.[1,2,8,12–14] In line with this, substances that increase dopamine signaling are effective in treating depression.[15,16] Similarly,

several theories propose a close link between extraversion and dopamine-related brain functions,[10,17] and some support for this assumption has emerged from pharmacological challenge studies linking questionnaire measures of extraversion to dopaminergic drug-evoked prolactin response.[18]

The individual experience of positive affect may further depend on one's expectations. The influence of expectations on affect is powerfully demonstrated in antidepressant placebo responses which have been reported in pharmacological and laboratory studies deliberately manipulating positive treatment expectations.[19] Moreover, it has been assumed that positive treatment expectations involve endogenous dopamine[20] and may be considered a type of reward response driven by expectations of clinical benefit. Some evidence of this emerges from Parkinson's disease research, where placebo responses have been linked to dopamine release and the strength of treatment expectations.[21] Further support stems from research linking reward system activation to placebo analgesia and its expectation.[22,23] Interestingly, greater placebo-induced dopamine release has been observed in depression non-remitters.[24]

Notably, individual differences in anhedonia, extraversion, and the broader construct of positive affectivity have not only been conceptually linked to the dopaminergic system, but have also been associated with the magnitude of placebo responses. These include optimism,[25] extraversion,[26–28] approach behavior,[29] and personality traits related to dopaminergic neurotransmission.[30] Moreover, individual variations in dopamine release in brain regions involved in reward encoding has been found to underlie placebo responses.[22] Given the association between dopamine-related variables and placebo responses, understanding such variables in depression may help tailor interventions more effectively.[31] However, while most existing studies have focused on pain,[32] research on antidepressant placebo responses is scarce.[33]

If and how individual differences in dopamine-related traits moderate antidepressant placebo responses is not clear, and competing hypotheses can be formulated. The placebo-reward hypothesis postulates that dopaminergic responsiveness may be crucial for placebo responses.[20] Linked to reduced dopamine functioning, high anhedonia might thus impede symptom improvement via placebo,[34] aligning with findings that traits negatively correlated to anhedonia (e.g., optimism and extraversion) predict stronger placebo responses.[26,35] On the other hand, positive treatment expectations may particularly enhance dopamine processing in individuals with high vs. low anhedonia, since expecting an increase in positive affect may be more rewarding to those with low positive affect/high anhedonia to begin with. Supporting this hypothesis, antidepressant treatment expectations have been found to reduce depressiveness-induced cardiac slowing in high anhedonia among healthy individuals.[36] Furthermore, lower optimism (linked to high anhedonia)[37] has been shown to predict better placebo treatment against stress in a healthy sample.[38] Thus, high anhedonia may predict either weaker or stronger placebo responses. However, while placebo responses among healthy individuals have been frequently reported in the context of various disorders, [22,23,25,26,28,30,35,36,38] research directly linking dopamine-related traits to antidepressant placebo responses is sparse.[36]

Depressive disorders involve dysfunctional affective experiences that come along with substantial limitations in well-being and daily functioning, posing a significant challenge in identifying and understanding successful treatment approaches. In order to gain insight into fundamental mechanisms and facilitate their translation into clinical applications, it is essential to examine specific dimensions of affective experiences (e.g., positive affect and dopaminergic functioning) in non-clinical individuals, given the potential for subclinical symptoms to evolve into clinical disorders. As such, the present study investigated the role of depression- and dopamine-related traits and dopamine in antidepressant placebo responses using a randomized,

double-blind, placebo-controlled 2×2 design with pharmacological (inert pills or dopamine D2 receptor antagonist sulpiride (400 mg)) and expectations (labels of either inactive or antidepressant) manipulations in *N* = 297 healthy individuals. We hypothesized that antidepressant treatment expectations would enhance state positive affect. Additionally, we hypothesized that these treatment expectation effects would involve the dopamine system, and accordingly be altered in the sulpiride vs. placebo substance group. We further assumed that treatment expectations effects would vary across individuals as a function of dopamine- and depression-related traits. As competing hypotheses, we specifically tested that higher anhedonia would relate to higher treatment expectation (i.e., placebo) effects[cf. 36] or to lower treatment expectation effects.[cf. 26] Finally, based on models linking trait anhedonia and extraversion to state positive affect via dopaminergic mechanisms, we explored whether sulpiride would alter the correlation between trait anhedonia (and extraversion) and state positive affect.

## Materials and methods

### Sample

A total of *N* = 297 healthy individuals (18-60 years, right-handed, German native speakers) participated in the study. Eligibility was determined through self-reports in a telephone interview. Exclusion criteria included: current psychiatric, neurological, autoimmune, hormonal, or cardiovascular conditions; any recent prescription medication use (past 3 months); pregnancy or hormonal contraception; liver, kidney, or bowel disorders; allergy to sulpiride, lactose, fructose, or gluten; regular smoking (> 1/week); alcohol or illegal substance abuse; excessive caffeine intake (> 8 cups/day); BMI < 19 or > 30. Informed consent was obtained prior to participation. The study, including the use of authorized deception, was approved by the Ethics Committee of Marburg University's Medical Department, following the Declaration of Helsinki.

Two participants were excluded prior to analysis due to abnormal prolactin levels (see Supplement), and 2 more due to missing baseline anhedonia scores, resulting in a final sample size of $N = 293$ (147 females; age: M = 25.13 years, SD = 4.2, range: 20-60). Group allocation was: $n = 73$ (no-substance expectation//placebo), $n = 74$ (no-substance expectation//sulpiride), $n = 72$ (antidepressant expectation//placebo), $n = 74$ (antidepressant expectation//sulpiride).

## Procedure

A detailed description of the entire procedure is included in the Supplement.

### *Procedure for the Experimental Session*

Participants arrived at 8 a.m. and provided a baseline blood sample (8 mL) to assess plasma prolactin levels, which were also measured after substance intake to test for drug response[39,40] (See Supplement for prolactin analyses). Participants were then administered 2 identical capsules along with standardized verbal instructions (see Supplement) manipulating treatment expectations. To induce antidepressant expectations, participants were told the capsules contained sulpiride, which would cause short-term mood enhancements noticeable after about 3 hours, even in individuals without depression. For no-substance expectations, the capsules were stated as inactive. After receiving the instructions, participants swallowed the capsules.

Regardless of expectations, either sulpiride (2×200 = 400 mg; Neuraxpharm, Germany) or placebo pills (Neuraxpharm, Germany) were administered, resulting in a 2×2 design with Expectation (antidepressant vs. no-substance) and Substance (placebo vs. sulpiride); both sulpiride and placebo capsules were visually identical. Group allocation followed a randomized, double-blind protocol. After pill intake, participants received a standardized vegan breakfast.

One hour after intake, the second blood sample (8 mL) was obtained. Approximately 2 hours and 45 minutes after intake, participants completed a 10-minute resting phase followed by

3 computer tasks: a probabilistic selection task,[41] an effort-based decision-making task,[42] and a musical mood induction procedure.[36] Before each task, participants were asked to complete a side effect questionnaire and indicate their treatment group. This was done to subtly reactivate the expectation manipulation throughout the session. Throughout the tasks, participants rated their affective states. At the session's end, participants reported which substance they believed to have received and rated their certainty on a scale of 0 = *placebo* to 10 = *sulpiride* (Table S2). All participants were then fully debriefed about the nature and purpose of the study, including any use of deception. The study was conducted in German and analyses of individual tasks including the mood induction procedure were preregistered at ClinicalTrials.gov; ID: NCT05208294 and will be reported elsewhere. In the current report, we present analyses on the entire experimental session which had not been preregistered.

***Substance***

Sulpiride is a selective dopamine D2 receptor antagonist generally well tolerated with a low affinity for histaminergic, cholinergic, serotonergic, adrenergic, or GABA receptors. Slowly absorbed from the gastrointestinal tract, sulpiride reaches peak serum levels approximately 3 hours after intake. Its elimination half-life averages 3 to 10 hours.[43] At low doses (50-200 mg), sulpiride presumably blocks presynaptic autoreceptors, elevating dopamine levels[44] and reducing depressive symptoms, while higher doses predominantly block postsynaptic receptors. Doses up to 800 mg induce minimal side effects, allowing blinded group allocation.[45] Here, 400 mg was employed, which should be sufficient to modulate dopaminergic processing[39] with minimal side effect risk.

**Questionnaire Measures**

***Anhedonia***

Within 2 days before the experiment, participants filled out online questionnaires including demographic data and trait measures. Trait anhedonia was assessed with a German adaptation of the 30-item Mood and Anxiety Symptom Questionnaire[46] (MASQ-D30),[47] which represents the tripartite model of mood[48] and contains General Distress, Anhedonic Depression, and Anxious Arousal scales. On a 5-point Likert scale (1 = *not at all* to 5 = *extremely*), the 10-item Anhedonic Depression scale measures lack of Positive Affect with items like "Felt really happy" and "Felt like I had a lot of energy". Higher reversed sum scores indicate higher Anhedonia, with excellent internal consistency in the present sample (Cronbach's $\alpha = .91$).

Anhedonia was also assessed via the German version[49] of the Snaith-Hamilton Pleasure Scale (SHAPS).[50] The internal consistency in the present healthy sample was $\alpha = .68$. Here, we report the measure with the higher internal consistency, i.e., MASQ-D30, as the primary measure of trait anhedonia. For comparability with other research, results of the SHAPS are also provided in the Supplement.

***Extraversion***

After breakfast on the testing day, participants completed the German[51] Big Five Aspect Scales (BFAS),[52] including a 20-item measure of Extraversion. Higher scores indicate higher Extraversion. Internal consistency was high ($\alpha = .88$). The Enthusiasm and Assertiveness facets were also computed for exploratory factor analysis (see below). ***Other Related Constructs***

Additionally, participants completed several other questionnaires assessing relevant constructs including: the German[53] revised Beck-Depression-Inventory (BDI-II),[54] the German[55] Temporal Experience of Pleasure Scale (TEPS),[56] the German[57] Life Orientation Test-Revised (LOT-R),[58] the behavioral approach system (BAS) scales of the German[59] Reinforcement

Sensitivity Theory of Personality Questionnaire (RST-PQ),[60i] the BAS scales of the German[61] Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS),[62] and a German Positive Valence Systems Scale (PVSS; own translation).[63]

**State Positive Affect**

Participants rated their current affective states via the German[64] Positive and Negative Affect Schedule (PANAS)[65] before substance intake (pre-Treatment). The PANAS included 20 items, with 10 each assessing Positive (e.g., "active", "interested") and Negative Affect on a 5-point Likert scale (1 = *not at all*, 5 = *extremely*). Before (T1) and at 4 subsequent time points during tasks and mood induction phases (T2-T5), participants repeated these ratings, resulting in 6 time points in total (Fig 1).

Given its relevance to anhedonia in depression, state positive affect assessed via PANAS is reported here. Results of PANAS Negative Affect and additional mood ratings (e.g., happiness, sadness; T1-T5) are included in the Supplement.

**Statistical Analyses**

All analyses were performed using R (v4.2.3) in RStudio.[66] Linear mixed-effects models were fitted using the lmer function of the lmerTest package,[67,68]with Time , Expectation, Substance, and Trait as fixed effects, and Subject as a random intercept. Omnibus tests (i.e., ANOVAs) were conducted on the fitted models using the following specification:

$$\text{State Positive Affect} \sim \text{Time} * \text{Expectation} * \text{Substance} * \text{Trait} + (1|\text{Subject}).$$

To examine whether substantial covariance among anhedonia, extraversion, and constructs related to dopamine and depression could be captured by any underlying factors

[i] Due to an oversight during the preparation of the questionnaires, an item of the Reward Reactivity subscale of the RST-PQ was missing, i.e., "I am especially sensitive to reward."

associated with placebo responses, an exploratory factor analysis (EFA) was conducted (jmv package's efa function) with Minimum Residuals and oblimin rotation. Eigenvalues > 1 were used for extraction. Factor scores were calculated with Thurstone estimation and included as a *z*-standardized continuous variable in the linear mixed-effects model. The following scales were included in the EFA: MASQ-D30 Anhedonic Depression, SHAPS-D, BFAS-Extraversion, BDI-II, TEPS, LOT-R, RSTPQ-BAS, BIS/BAS, and PVSS (Table 2).

## Results

Baseline anhedonia scores in the current sample, averaged across all groups, were comparable with a healthy sample in our previous study, which demonstrated antidepressant placebo responses among participants high in anhedonia.[36ii] Separate ANOVAs including experimental conditions as factor confirmed that baseline traits scores and age did not differ across groups (Table 1). Descriptive statistics including mean, standard deviation, and range across all administered questionnaires are reported in Table S1. There were no significant between-group differences across these measures (all $p > .29$).

### Manipulation Check

#### *Substance Manipulation*

[ii] With regard to restricted variability, we observed a standard deviation in the MASQ-D30 Anhedonia of SD = 7.4, whereas another study reported an SD of 8.9 in a presumably more representative sample (N = 5341).[69] To assess whether this restricted variability may have attenuated the observed correlations between anhedonia and state positive affect, we applied Thorndike's Case II correction[70] using SD = 8.9 as a reference. Expectedly, the strength of the correlations increased across all time points after correction, suggesting that the true associations may—if anything—be underestimated in the observed data (pre-Treatment: from $r = -.33$ to $r = -.40$; T1: -.27 to -.33, T2: -.21 to -.26; T3: -.18 to -.22; T4: -.17 to -.21; T5: -.18 to -.22). This supports the interpretation that anhedonia is meaningfully associated with momentary affective experience, even within a restricted range.

A Substance × Expectation ANOVA on participants' plasma prolactin change confirmed the expected main effect of Substance ($F(1, 193) = 269.97$, $p < .001$), such that the placebo group had a smaller change (M = -1.18, SD = 2.00) than the sulpiride group (M = 62.50, SD = 38.0), $t(99) = -16.72$, $p < .001$. Expectation did not affect prolactin levels ($F(1, 193) = 2.04$, $p = .155$); plasma prolactin levels for all participants are plotted in Fig S1.

We additionally tested the associations between sex, body weight, and prolactin change and found a larger prolactin increase in females compared to males ($p < .001$; see Supplement). Finally, testing whether sulpiride-induced changes in plasma prolactin were associated with trait anhedonia and extraversion[9] revealed no significant associations (see Supplement).

***Expectation Manipulation***

A Substance × Expectation ANOVA on the self-rated belief to have received an inert pill vs. sulpiride confirmed a significant main effect of Expectation ($F(1, 495) = 86.39$, $p < .001$), such that participants in the antidepressant expectation group were more likely to believe that they had received sulpiride than the no-substance expectation group.

Additionally, both Expectation ($p = .670$) and Substance ($p = .220$) manipulation did not predict post-Treatment self-reported side effects (see Supplement).

**State Positive Affect over Time**

***Anhedonia***

The omnibus test of the model on positive affect ratings revealed a main effect of Time ($F(5, 1419) = 84.07$, $p < .001$, $\eta^2_p = .229$), indicating that positive affect varied significantly across time points. Estimated marginal means (EMM) revealed that state positive affect decreased from pre-Treatment (EMM = 2.72, SE = 0.04) to T1 (EMM = 2.42, SE = 0.04), then gradually increased throughout T2 (EMM = 2.57, SE = 0.04), peaking at T3 (EMM = 2.76, SE =

0.04), and subsequently declined at T4 (EMM = 2.53, SE = 0.04), with the lowest during T5 (EMM = 2.06, SE = 0.04)(see Supplement). There was also a main effect of Anhedonia ($F$(1, 285) = 21.37, $p < .001$, $\eta^2_p = .070$) indicating lower state positive affect in high anhedonia. In contrast to our hypotheses, no main effects of Expectation and Substance, and no Expectation × Substance interaction were observed across the sample ($p > .273$). However, we observed a Substance × Anhedonia interaction ($F$(1, 285) = 7.19, $p = .008$, $\eta^2_p = .025$) further qualified by a Substance × Anhedonia × Time interaction, $F$(5, 1419) = 2.23, $p = .049$, $\eta^2_p = .008$.

To further investigate this 3-way interaction, follow-up Pearson correlations between anhedonia and state positive affect were computed for each time point and substance group. Pre-Treatment, there was an expected negative association for both groups, such that lower positive affect ratings were associated with higher anhedonia (placebo: $r$(141) = -0.41, $p < .001$; sulpiride: $r$(143) = -0.24, $p = .004$; $Z$ = -1.65, $p = .098$; Fig 2). This negative association persisted under placebo. Under sulpiride, however, it decreased from pre-Treatment ($r$ = -0.24, $p < .05$) over T1 (approximately 3 hours post-intake; $r$ = -0.16, $p = .050$) to T2 ($r$ = -0.16, $p = .060$), T3 ($r$ = -0.05, $p = .512$), T4 ($r$ = 0.01, $p = .939$), and T5 ($r$ = 0.03, $p = .685$). Fisher's $Z$ tests revealed that significant correlation differences between substance groups emerged at T3 ($Z$ = -2.25, $p = .025$) and persisted throughout T4 ($Z$ = -2.86, $p = .004$) and T5 ($Z$ = -3.51, $p < .001$), while they were absent before substance intake (pre-Treatment: $Z$ = -1.65, $p = .098$) and shortly after (T1: $Z$ = -1.91, $p = .056$) and T2 ($Z$ = -0.93, $p = .353$; Fig 2). No other effects emerged (all $p > .192$; Table S2). Similar patterns were observed for SHAPS-D and BDI-II (see Supplement).

To test the specificity of Anhedonia, separate omnibus tests on the models were additionally conducted with MASQ-D30 Anxious Arousal and General Distress subscales in place of Anhedonia scores. These models did not yield similar results (see Supplement).

***Extraversion***

In line with prior research,[71-73] anhedonia and extraversion were negatively correlated in the present sample ($r(290) = -0.54$, $p < .001$). Given its negative association with anhedonia[71-73] and positive association with positive affect,[74] we tested whether an omnibus test on the model with Extraversion as z-standardized continuous variable would reveal comparable effects to Anhedonia. The omnibus test revealed main effects of Time ($F(5, 1415) = 82.66$, $p < .001$, $\eta^2_p = .226$) and Extraversion ($F(1, 284) = 10.05$, $p = .002$, $\eta^2_p = .034$), a trend Substance × Extraversion interaction ($F(1, 284) = 3.73$, $p = .054$, $\eta^2_p = .013$), and a Time × Expectation × Extraversion interaction ($F(5, 1415) = 3.68$, $p = .003$, $\eta^2_p = .013$). The 3-way interaction indicated that the expected positive association between Extraversion and positive affect which was observed pre-treatment ($r(286) = 0.27$, $p < .001$) only persisted under no-substance expectations, but diminished from T2 to T4 due to relative increases in introverts' positive affect under antidepressant vs. no-substance expectations (Fig 3). Thus, in line with our hypothesis, antidepressant treatment expectations raised positive affect for introverts but not for extraverts.

Although the Substance × Extraversion interaction was not significant here, we explored whether the association between Extraversion and positive affect over time indicated a similar susceptibility to the pharmacological manipulation as Anhedonia. As shown in the supplement, a comparable result pattern was observed.

***Factor Extracted from EFA***

The EFA of 16 different anhedonia and extraversion scales revealed 1 factor with Eigenvalue > 1 (4.830; subsequent Eigenvalues: 0.881, 0.757), which we term Positive Affectivity. Factor loadings are summarized in Table 2. The omnibus test on the model revealed main effects of Time ($F(5, 1398) = 87.41$, $p < .001$, $\eta^2_p = .238$) and Positive Affectivity ($F(1, 280) = 20.20$, $p < .001$, $\eta^2_p = .067$), a Substance × Positive Affectivity interaction ($F(1, 280) = 7.68$, $p = .006$, $\eta^2_p = .027$), and a Time × Expectation × Positive Affectivity interaction ($F(5,$

1398) = 2.34, $p$ = .040, $\eta^2_p$ = .008). Like Anhedonia and Extraversion, Positive Affectivity was positively associated with positive affect across substance groups pre-treatment, $r(285) = 0.35$, $p < .001$. Post-treatment (i.e., for T1-T4), this association persisted over time for placebo ($r(142) = 0.36$, $p < .001$) but not sulpiride ($r(141) = 0.09$, $p = .147$; $Z = 2.39$)(Fig S2). Moreover, the 3-way interaction indicated that this positive association persisted from pre-Treatment to T4 under no-substance expectations ($r = 0.29$), but diminished at T3 under antidepressant expectations ($r = 0.07$; $Z = 1.87$)(Fig S3). Thus, the correlation between a general trait Positive Affectivity factor and state positive affect ratings was initially present in the entire sample but then disrupted by both sulpiride and antidepressant treatment expectations. Correlation Coefficients for all questionnaires included in the EFA are included in Table S4. No further effects emerged (all $p > .096$).

## Discussion

This study sought to examine the complex interplay of dopamine, expectations, and positive affect-related personality traits on state positive affect. In a 2×2 placebo-controlled design involving pharmacological and expectation manipulation in a large sample, we found that the effects of the experimental treatment expectation manipulation and sulpiride crucially depended on individual differences in Extraversion and Anhedonia, respectively, or, more generally, on a broad Positive Affectivity factor. Contrary to our expectations, no main effects of treatment expectation or sulpiride were observed. The observed interactions indicate that antidepressant treatment expectations and sulpiride particularly raise state positive affect in individuals with low positive affective traits.

### Antidepressant Treatment Expectation Effects in Low Positive Affectivity

Antidepressant treatment expectations did not enhance state positive affect across the board as we hypothesized. Rather, antidepressant treatment expectations increased state positive

affect among introverts during T2-T4, as evidenced in a disruption of the prototypical correlation of extraversion and state positive affect during these time windows. A similar pattern (albeit non-significant) emerged for anhedonia, such that its negative association with state positive affect decreased at T3 under antidepressant expectations. Finally, a trait × Expectation interaction also emerged for the broad Positive Affectivity factor that captured the covariance of various extraversion and anhedonia scales. Initially, Positive Affectivity was correlated with state positive affect, but antidepressant treatment expectations selectively enhanced state positive affect in individuals with low Positive Affectivity. These observations align with our previous findings that antidepressant expectations attenuated depressiveness-induced cardiac slowing in high vs. low anhedonia[36] and supports our hypothesis that higher anhedonia (or lower Positive Affectivity) facilitate antidepressant treatment expectation effects. They further converge with prior findings that lower extraversion predicted stronger placebo responses against stress,[38] and that novelty seeking, an extraversion- and dopamine-related trait, was lower in individuals susceptible to placebo-induced sensations.[75] At the same time, this group of results contrasts with studies suggesting that higher extraversion[26,27] and optimism[25] predict stronger placebo responses. Notably, these diverging findings mostly focused on pain rather than state positive affect. Thus, optimism may facilitate placebo analgesia but may not generalize to depression-related placebo responses, in which lower levels of positive affect may be necessary to motivate mood enhancements. Aligning with the association between low extraversion and depressive symptoms (i.e., anhedonia),[71-73] our findings demonstrate that dopamine- and depression-related traits moderate antidepressant placebo responses, which may hinge on depressiveness magnitude. Moreover, no expectation effects were revealed with anxiety-related scales (see Supplement), underscoring the specificity of low positive affectivity. While domain-specific research remains inconclusive and scarce,[33] our findings highlight the role of individual differences in

antidepressant placebo responses, underscoring the importance to probe variables relevant to depression.

**Effects of Dopaminergic Substance Parallel Treatment Expectation**

Sulpiride increased state positive affect in participants with high vs. low anhedonia. Similar patterns emerged for extraversion and Positive Affectivity, such that sulpiride raised introverts' lower state positive affect, while reducing extraverts' higher baseline positive affect. Likewise, there was a positive association between Positive Affectivity and state positive affect before treatment, which was disrupted by sulpiride: state positive affect was elevated among participants with lower Positive Affectivity, whereas it was decreased in higher levels.

Our results suggest that sulpiride may have an equally-breaking effect on state positive affect, i.e., increasing in individuals with higher anhedonia, while decreasing in lower anhedonia. This aligns with prior research indicating paradoxical (U-shaped) effects of dopamine manipulation depending on baseline characteristics.[e.g., 11,76,77] While its underlying mechanism remains debated,[e.g., 78–80] sulpiride may enhance mood in high anhedonic individuals by compensating for lower baseline dopamine signaling. Conversely, individuals with lower anhedonia and intact dopamine functioning may experience reduced positive affect due to sulpiride's postsynaptic action, which presumably reduced dopamine signaling. This effect may be smaller in high anhedonia due to relative blunted baseline responsiveness. Accordingly, sulpiride has been shown to produce antidepressant effects in mild to moderate depression[16] and increase positive affect among introverts.[11] Moreover, 400 mg sulpiride has been reported to enhance motivation specifically in low dopamine synthesis capacity.[78] While another study reported attenuated hedonic responses to pleasant stimuli following D2 receptor antagonist intake, baseline traits were not considered.[81]

To some degree, the observed pharmacological effects parallel the previously discussed antidepressant expectation effects: both manipulations disrupted the correlations between state positive affect and extraversion, anhedonia, and Positive Affectivity. The similarity of these patterns provides support for the assumption that treatment expectation effects involve the dopamine system and are altered under sulpiride, i.e., dopamine manipulation enhanced state positive affect in participants with relative high anhedonia levels, while producing contrasting effects in lower anhedonia levels. We speculate that high anhedonia is related to relative lower dopamine sensitivity, whereas individuals with low anhedonia have relatively higher dopamine signaling. Moreover, our results are consistent with the notion that the link between dopamine and anhedonia is not limited to the motivational component but may also involve the pleasure-related facet of anhedonia, as indicated by a converging result pattern when the Consummatory Pleasure of the TEPS, a scale presumably reflecting pleasure aspects of anhedonia, was analyzed (see Supplement). In sum, our findings suggest that individual differences in dopaminergic functioning modulate antidepressant placebo responses[e.g.,22,23] and contribute to research on neurobiological mechanisms underlying such responses.

Interestingly, however, no significant interaction between substance and expectation manipulation was observed. If placebo responses were driven by dopamine, the expectation manipulation effects may have been disrupted by sulpiride as hypothesized, especially given the presumably high dosage of 400 mg. As this was not the case, a possible interpretation is that sulpiride acted not only as an antagonist via postsynaptic blockade among all participants, but may also have exhibited agonist-like effects through blocking presynaptic autoreceptors.[cf.78] Additionally, while both dopaminergic and expectation manipulation increased state positive affect in individuals with low Positive Affectivity, they may rely on only partially overlapping

neural systems (e.g., involved in more subtle experience vs. more explicit ratings of affect, respectively), allowing their effects to remain independent to some extent.

**Implications**

Previous research has shown substantial evidence for expectation-induced placebo responses in both healthy and depressed participants.[e.g.,82–84] A recent meta-analysis further confirmed consistent effects across treatment modalities.[85] However, most evidence emerges from clinical settings and centers on pain.[86] Understanding whether antidepressant placebo responses differ between healthy and clinically diagnosed individuals remains limited. Our study, employing a pharmacological challenge in a large, healthy sample, demonstrates that such responses may hinge on depressiveness magnitude and the presence of depressive experience. Additionally, the effects observed in the present study are specific to positive affect and do not emerge for negative affect (see Supplement). While most studies focus on negative affective experiences,[83,84,87,88] targeting positive affect may be particularly relevant for anhedonia and reward hyposensitivity as central aspects of depression.[36,89,90]

Limited research has specifically examined the link between dopamine functioning and affective experience, and existing studies rarely assess relevant baseline traits.[81,91–93] Our study offers valuable insights into how individual differences in these traits moderate dopaminergic drugs effects on mood.[94] Furthermore, the observed pattern for Positive Affectivity reflects the effects of both treatment expectations and sulpiride, supporting our assumption that anhedonia, depression, and dopamine functioning are key factors in these responses.

**Limitations and Conclusions**

Antidepressant placebo and substance responses were observed only among participants with lower Positive Affectivity (i.e., lower extraversion/higher anhedonia). While we interpret

this as highlighting the role of individual differences, an alternative interpretation is that there may have been ceiling effects such that high treatment expectations and/or sulpiride could not further enhance positive affect in healthy individuals with higher Positive Affectivity. However, this interpretation would be at odds with the observation that sulpiride and antidepressant treatment expectations tended to decrease (rather than maintain) state positive affect in low anhedonia and high extraversion, respectively. A second limitation may be that the experimental expectation manipulation was not sufficiently convincing for all participants, especially in a university setting where healthy participants were familiar with such setups. However, manipulation checks confirmed the effectiveness of the manipulation at the group level, and control analyses excluding participants who did not believe the instructed treatment yielded comparable results (see Supplement). Thus, these results support our interpretation that a certain depressiveness magnitude is required for consistent antidepressant placebo responses in healthy participants.[36] Future studies could explore this mechanism in more clinically diverse populations, allowing direct comparisons between healthy and diagnosed individuals.

This study is among the first to investigate how depression- and dopamine-related traits moderate antidepressant placebo responses, employing a pharmacological challenge in a large, healthy sample. Our findings indicate that low dispositional positive affectivity may be necessary for robust antidepressant placebo responses. Additionally, while dopamine functioning is essential for the underlying psychopharmacological mechanisms, baseline traits may influence the effects of dopamine antagonists. Taken together, our study highlights the weight of individual differences in both therapeutic and pharmacological approaches to depression treatment. Future research should consider these factors to develop more effective, tailored interventions.

## Data Availability Statement

The data underlying this article can be made available upon reasonable request to the corresponding author.

## Author Contributions

LCC: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. NA: Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration. PB: Writing – review & editing. TL: Writing – review & editing. DAP: Writing – review & editing. DE: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. EMM: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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## Competing Interests

Over the past three years, Dr. Pizzagalli has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Sage Therapeutics, Sama Therapeutics, and Takeda; he has received honoraria from the American Psychological

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## References


1. Pizzagalli DA. Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annu Rev Clin Psychol*. 2014;10(1):393-423. doi:10.1146/annurev-clinpsy-050212-185606

2. Treadway MT, Zald DH. Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2011;35(3):537-555. doi:10.1016/j.neubiorev.2010.06.006

3. Lucas RE, Baird BM. Extraversion and Emotional Reactivity. *J Pers Soc Psychol*. 2004;86(3):473-485. doi:10.1037/0022-3514.86.3.473

4. Smillie LD, Cooper AJ, Wilt J, Revelle W. Do extraverts get more bang for the buck? Refining the affective-reactivity hypothesis of extraversion. *J Pers Soc Psychol*. 2012;103(2):306-326. doi:10.1037/a0028372

5. Watson D, Tellegen A. Toward a consensual structure of mood. *Psychol Bull*. 1985;98(2):219-235. doi:10.1037/0033-2909.98.2.219

6. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 Countries between 1994 and 2014. *Sci Rep*. 2018;8(1):2861. doi:10.1038/s41598-018-21243-x

7. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. *J Psychiatr Res*. 2020;126:134-140. doi:10.1016/j.jpsychires.2019.08.002

8. Huys QJ, Pizzagalli DA, Bogdan R, Dayan P. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biol Mood Anxiety Disord*. 2013;3(1):12. doi:10.1186/2045-5380-3-12

9. Monreal JA, Duval F, Mokrani MC, Fattah S, Palao D. Differences in multihormonal responses to the dopamine agonist apomorphine between unipolar and bipolar depressed patients. *J Psychiatr Res*. 2019;112:18-22. doi:10.1016/j.jpsychires.2019.02.009

10. Depue RA, Collins PF. Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *Behav Brain Sci*. 1999;22(3):491-517. doi:10.1017/S0140525X99002046

11. Mueller EM, Burgdorf C, Chavanon ML, Schweiger D, Wacker J, Stemmler G. Dopamine modulates frontomedial failure processing of agentic introverts versus extraverts in incentive contexts. *Cogn Affect Behav Neurosci*. 2014;14(2):756-768. doi:10.3758/s13415-013-0228-9

12. Zald DH, Boileau I, El-Dearedy W, et al. Dopamine Transmission in the Human Striatum during Monetary Reward Tasks. *J Neurosci*. 2004;24(17):4105-4112. doi:10.1523/JNEUROSCI.4643-03.2004

13. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)*. 2007;191(3):391-431. doi:10.1007/s00213-006-0578-x

14. Wise RA. Dopamine and reward: The anhedonia hypothesis 30 years on. *Neurotox Res*. 2008;14(2-3):169-183. doi:10.1007/BF03033808

15. Willner P, Hale AS, Argyropoulos S. Dopaminergic mechanism of antidepressant action in depressed patients. *J Affect Disord*. 2005;86(1):37-45. doi:10.1016/j.jad.2004.12.010

16. Rüther E, Degner D, Munzel U, et al. Antidepressant Action of Sulpiride. Results of a Placebo-Controlled Double-Blind Trial. *Pharmacopsychiatry*. 1999;32(04):127-135. doi:10.1055/s-2007-979218

17. DeYoung CG. Cybernetic Big Five Theory. *J Res Pers*. 2015;56:33-58. doi:10.1016/j.jrp.2014.07.004

18. Fitzgerald P, Dinan TG. Prolactin and dopamine: What is the connection? A Review Article. *J Psychopharmacol*. 2008;22(2_suppl):12-19. doi:10.1177/0269216307087148

19. Petrie KJ, Rief W. Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. *Annu Rev Psychol*. 2019;70(1):599-625. doi:10.1146/annurev-psych-010418-102907

20. de la Fuente-Fernández R. The placebo-reward hypothesis: dopamine and the placebo effect. *Parkinsonism Relat Disord*. 2009;15:S72-S74. doi:10.1016/S1353-8020(09)70785-0

21. Lidstone SC, Schulzer M, Dinelle K, et al. Effects of Expectation on Placebo-Induced Dopamine Release in Parkinson Disease. *Arch Gen Psychiatry*. 2010;67(8):857. doi:10.1001/archgenpsychiatry.2010.88

22. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and Nocebo Effects Are Defined by Opposite Opioid and Dopaminergic Responses. *Arch Gen Psychiatry*. 2008;65(2):220. doi:10.1001/archgenpsychiatry.2007.34

23. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Individual Differences in Reward Responding Explain Placebo-Induced Expectations and Effects. *Neuron*. 2007;55(2):325-336. doi:10.1016/j.neuron.2007.06.028

24. Peciña M, Sikora M, Avery ET, et al. Striatal dopamine D2/3 receptor-mediated neurotransmission in major depression: Implications for anhedonia, anxiety and treatment response. *Eur Neuropsychopharmacol*. 2017;27(10):977-986. doi:10.1016/j.euroneuro.2017.08.427

25. Kern A, Kramm C, Witt CM, Barth J. The influence of personality traits on the placebo/nocebo response. *J Psychosom Res*. 2020;128:109866. doi:10.1016/j.jpsychores.2019.109866

26. Beedie CJ, Foad AJ, Coleman DA. Identification of placebo responsive participants in 40km laboratory cycling performance. *J Sports Sci Med*. 2008;7(1):166-175.

27. Kelley JM, Lembo AJ, Ablon JS, et al. Patient and practitioner influences on the placebo effect in irritable bowel syndrome. *Psychosom Med*. 2009;71(7):789-797. doi:10.1097/PSY.0b013e3181acee12

28. Morton DL, Watson A, El-Deredy W, Jones AKP. Reproducibility of placebo analgesia: Effect of dispositional optimism. *Pain*. 2009;146(1):194-198. doi:10.1016/j.pain.2009.07.026

29. Vecchio A, De Pascalis V. Approach and avoidance personality traits in acute pain and placebo analgesia. *Pers Individ Dif*. 2021;169:109830. doi:10.1016/j.paid.2020.109830

30. Schweinhardt P, Seminowicz DA, Jaeger E, Duncan GH, Bushnell MC. The anatomy of the mesolimbic reward system: A link between personality and the placebo analgesic response. *J Neurosci*. 2009;29(15):4882-4887. doi:10.1523/JNEUROSCI.5634-08.2009

31. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-bio-ehavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. Michel MC, ed. *Pharmacol Rev*. 2015;67(3):697-730. doi:10.1124/pr.114.009423

32. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. *Front Psychol*. 2014;5. doi:10.3389/fpsyg.2014.01079

33. Zaharia S, Horosan L. Quantifying placebo and nocebo responses: A narrative review of implications for clinical practice and research in psychiatry. *Ro J Psychiatry Psychother*. 2021;23(4):119-128. doi:10.37897/RJPP.2021.4.3

34. Trivedi MH, South C, Jha MK, et al. A novel strategy to identify placebo responders: Prediction index of clinical and biological markers in the EMBARC trial. *Psychother Psychosom*. 2018;87(5):285-295. doi:10.1159/000491093

35. Geers AL, Wellman JA, Fowler SL, Helfer SG, France CR. Dispositional Optimism Predicts Placebo Analgesia. *J Pain*. 2010;11(11):1165-1171. doi:10.1016/j.jpain.2010.02.014

36. Chuang LC, Panitz C, Mueller EM. Interindividual differences in anhedonia moderate antidepressant placebo responses on heart rate in healthy individuals. *J Affect Disord Rep*. 2024;15:100705. doi:10.1016/j.jadr.2023.100705

37. Rygula R, Papciak J, Popik P. Trait Pessimism Predicts Vulnerability to Stress-Induced Anhedonia in Rats. *Neuropsychopharmacol*. 2013;38(11):2188-2196. doi:10.1038/npp.2013.116

38. Darragh M, Booth RJ, Consedine NS. Investigating the 'placebo personality' outside the pain paradigm. *J Psychosom Res*. 2014;76(5):414-421. doi:10.1016/j.jpsychores.2014.02.011

39. Mehta MA, Montgomery AJ, Kitamura Y, Grasby PM. Dopamine D2 receptor occupancy levels of acute sulpiride challenges that produce working memory and learning impairments in healthy volunteers. *Psychopharmacology (Berl)*. 2008;196(1):157-165. doi:10.1007/s00213-007-0947-0

40. Bell C, Bhikha S, Colhoun H, Carter F, Frampton C, Porter R. The response to sulpiride in social anxiety disorder: D2 receptor function. *J Psychopharmacol*. 2013;27(2):146-151. doi:10.1177/0269881112450778

41. Frank MJ, Seeberger LC, O'Reilly RC. By Carrot or by Stick: Cognitive Reinforcement Learning in Parkinsonism. *Science*. 2004;306(5703):1940-1943. doi:10.1126/science.1102941

42. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The Effort Expenditure for Rewards Task as an Objective Measure of Motivation and Anhedonia. García AV, ed. *PLoS One*. 2009;4(8):e6598. doi:10.1371/journal.pone.0006598

43. Mauri MC, Bravin S, Bitetto A, Rudelli R, Invernizzi G. A Risk-Benefit Assessment of Sulpiride in the Treatment of Schizophrenia: *Drug Saf*. 1996;14(5):288-298. doi:10.2165/00002018-199614050-00003

44. Kuroki T, Meltzer HY, Ichikawa J. Effects of Antipsychotic Drugs on Extracellular Dopamine Levels in Rat Medial Prefrontal Cortex and Nucleus Accumbens. *J Pharmacol Exp Ther*. 1999;288(2):774-781.

45. Eisenegger C, Naef M, Linssen A, et al. Role of Dopamine D2 Receptors in Human Reinforcement Learning. *Neuropsychopharmacol*. 2014;39(10):2366-2375. doi:10.1038/npp.2014.84

46. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *J Abnorm Psychol*. 1995;104(1):3-14. doi:10.1037/0021-843X.104.1.3

47. Wardenaar KJ, Van Veen T, Giltay EJ, De Beurs E, Penninx BWJH, Zitman FG. Development and validation of a 30-item short adaptation of the mood and anxiety symptoms questionnaire (MASQ). *Psychiatry Res*. 2010;179(1):101-106. doi:10.1016/j.psychres.2009.03.005

48. Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm Psychol*. 1991;100(3):316-336. doi:10.1037/0021-843X.100.3.316

49. Franz M, Lemke M, Meyer T, Ulferts J, Puhl P, Snaith R. Deutsche Version der Snaith-Hamilton-Pleasure-Scale (SHAPS-D). *Fortschr Neurol Psychiatr*. 1998;66(09):407-413. doi:10.1055/s-2007-995279

50. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A Scale for the Assessment of Hedonic Tone the Snaith–Hamilton Pleasure Scale. *Br J Psychiatry*. 1995;167(1):99-103. doi:10.1192/bjp.167.1.99

51. Mussel P, Paelecke M. BFAS-G - Big Five Aspect Scales - German. Published online 2018. doi:10.23668/PSYCHARCHIVES.4535

52. DeYoung CG, Quilty LC, Peterson JB. Between facets and domains: 10 aspects of the Big Five. *J Pers Soc Psychol*. 2007;93(5):880-896. doi:10.1037/0022-3514.93.5.880

53. Hautzinger M, Keller F, Kühner C. *Beck-Depressions-Inventar - Revision.* Pearson; 2006.

54. Beck AT, Steer RA, Brown G. Beck Depression Inventory–II. Published online 1996. doi:10.1037/t00742-000

55. Simon JJ, Zimmermann J, Cordeiro SA, et al. Psychometric evaluation of the Temporal Experience of Pleasure Scale (TEPS) in a German sample. *Psychiatry Res*. 2018;260:138-143. doi:10.1016/j.psychres.2017.11.060

56. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: A scale development study. *J Res Per*. 2006;40(6):1086-1102. doi:10.1016/j.jrp.2005.11.001

57. Glaesmer H, Hoyer J, Klotsche J, Herzberg PY. Die deutsche Version des Life-Orientation-Tests (LOT-R) zum dispositionellen Optimismus und Pessimismus. *Zeitschrift für Gesundheitspsychologie*. 2008;16(1):26-31. doi:10.1026/0943-8149.16.1.26

58. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the life orientation test. *J Pers Soc Psychol*. 1994;67(6):1063-1078. doi:10.1037/0022-3514.67.6.1063

59. Pugnaghi G, Cooper A, Ettinger U, Corr PJ. The Psychometric Properties of the German Language Reinforcement Sensitivity Theory-Personality Questionnaire (RST-PQ). *J Individ Differ*. 2018;39(3):182-190. doi:10.1027/1614-0001/a000262

60. Corr PJ, Cooper AJ. The Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ): Development and validation. *Psychol Assess*. 2016;28(11):1427-1440. doi:10.1037/pas0000273

61. Strobel A, Beauducel A, Debener S, Brocke B. Eine deutschsprachige Version des BIS/BAS-Fragebogens von Carver und White. *Zeitschrift für Differentielle und Diagnostische Psychologie*. 2001;22(3):216-227. doi:10.1024//0170-1789.22.3.216

62. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *J Pers Soc Psychol*. 1994;67(2):319-333. doi:10.1037/0022-3514.67.2.319

63. Khazanov GK, Ruscio AM, Forbes CN. The Positive Valence Systems Scale: Development and Validation. *Assessment*. 2020;27(5):1045-1069. doi:10.1177/1073191119869836

64. Breyer B, Bluemke M. Deutsche Version der Positive and Negative Affect Schedule PANAS (GESIS Panel). *Zusammenstellung sozialwissenschaftlicher Items und Skalen (ZIS)*. Published online 2016. doi:10.6102/ZIS242

65. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070. doi:10.1037/0022-3514.54.6.1063

66. R Core Team. R: A language and environment for statistical computing. Published online 2023. https://www.R-project.org/

67. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using **lme4**. *J Stat Softw*. 2015;67(1). doi:10.18637/jss.v067.i01

68. Kuznetsova A, Brockhoff PB, Christensen RHB. **lmerTest** package: Tests in linear mixed effects models. *J Stat Soft*. 2017;82(13). doi:10.18637/jss.v082.i13

69. Louter MA, Pijpers JA, Wardenaar KJ, et al. Symptom dimensions of affective disorders in migraine patients. *J Psychosom Res*. 2015;79(5):458-463. doi:10.1016/j.jpsychores.2015.09.014

70. Thorndike RL. *Personnel Selection: Test and Measurement Techniques.* Wiley; 1949. https://psycnet.apa.org/record/1949-05074-000

71. Langvik E, Borgen Austad S. Psychometric Properties of the Snaith–Hamilton Pleasure Scale and a Facet-Level Analysis of the Relationship Between Anhedonia and Extraversion in a Nonclinical Sample. *Psychol Rep*. 2019;122(1):360-375. doi:10.1177/0033294118756336

72. Mueller EM, Panitz C, Pizzagalli DA, Hermann C, Wacker J. Midline theta dissociates agentic extraversion and anhedonic depression. *Pers Individ Dif*. 2015;79:172-177. doi:10.1016/j.paid.2014.10.043

73. Watson D, Clark LA, Khoo S. The temperamental basis of extraversion and its implications for psychopathology. *Per Individ Dif*. 2022;185:111302. doi:10.1016/j.paid.2021.111302

74. Smillie LD, DeYoung CG, Hall PJ. Clarifying the Relation Between Extraversion and Positive Affect. *J Pers*. 2015;83(5):564-574. doi:10.1111/jopy.12138

75. Beissner F, Brünner F, Fink M, Meissner K, Kaptchuk TJ, Napadow V. Placebo-induced somatic sensations: A multi-modal study of three different placebo interventions. Antal A, ed. *PLoS One*. 2015;10(4):e0124808. doi:10.1371/journal.pone.0124808

76. Chavanon ML, Wacker J, Stemmler G. Paradoxical dopaminergic drug effects in extraversion: dose- and time-dependent effects of sulpiride on EEG theta activity. *Front Hum Neurosci*. 2013;7. doi:10.3389/fnhum.2013.00117

77. Van Den Bosch R, Lambregts B, Määttä J, et al. Striatal dopamine dissociates methylphenidate effects on value-based versus surprise-based reversal learning. *Nat Commun*. 2022;13(1):4962. doi:10.1038/s41467-022-32679-1

78. Westbrook A, Van Den Bosch R, Määttä JI, et al. Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. *Science*. 2020;367(6484):1362-1366. doi:10.1126/science.aaz5891

79. Mehta MA, Hinton EC, Montgomery AJ, Bantick RA, Grasby PM. Sulpiride and mnemonic function: effects of a dopamine D2 receptor antagonist on working memory, emotional

memory and long-term memory in healthy volunteers. *J Psychopharmacol*. 2005;19(1):29-38. doi:10.1177/0269881105048889

80. Naef M, Müller U, Linssen A, Clark L, Robbins TW, Eisenegger C. Effects of dopamine D2/D3 receptor antagonism on human planning and spatial working memory. *Transl Psychiatry*. 2017;7(4):e1107-e1107. doi:10.1038/tp.2017.56

81. Berg M, Riehle M, Rief W, Lincoln T. Does partial blockade of dopamine D2 receptors with Amisulpride cause anhedonia? An experimental study in healthy volunteers. *J Psychiatr Res*. 2023;158:409-416. doi:10.1016/j.jpsychires.2023.01.014

82. Baker J, Gamer M, Rauh J, Brassen S. Placebo induced expectations of mood enhancement generate a positivity effect in emotional processing. *Sci Rep*. 2022;12(1):5345. doi:10.1038/s41598-022-09342-2

83. Glombiewski JA, Rheker J, Wittkowski J, Rebstock R, Rief W. Placebo mechanisms in depression: An experimental investigation of the impact of expectations on sadness in female participants. *J Affect Disord*. 2019;256:658-667. doi:10.1016/j.jad.2019.06.070

84. Haas JW, Rief W, Glombiewski JA, Winkler A, Doering BK. Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *J Affect Disord*. 2020;274:920-928. doi:10.1016/j.jad.2020.05.056

85. Jones BDM, Razza LB, Weissman CR, et al. Magnitude of the Placebo Response Across Treatment Modalities Used for Treatment-Resistant Depression in Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2021;4(9):e2125531. doi:10.1001/jamanetworkopen.2021.25531

86. Tu Y, Zhang L, Kong J. Placebo and nocebo effects: from observation to harnessing and clinical application. *Transl Psychiatry*. 2022;12(1):524. doi:10.1038/s41398-022-02293-2

87. Göhler AC, Haas JW, Sperl MFJ, Hermann C, Winkler A. Placebo nasal spray protects female participants from experimentally induced sadness and concomitant changes in autonomic arousal. *J Affect Disord*. 2021;295:131-138. doi:10.1016/j.jad.2021.07.037

88. Rebstock L, Schäfer LN, Kube T, Ehmke V, Rief W. Placebo prevents rumination: An experimental study. *J Affect Disord*. 2020;274:1152-1160. doi:10.1016/j.jad.2020.06.010

89. Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: A neuroscience driven approach. *Depress Anxiety*. 2016;33(10):927-938. doi:10.1002/da.22490

90. Craske MG, Meuret AE, Echiverri-Cohen A, Rosenfield D, Ritz T. Positive affect treatment targets reward sensitivity: A randomized controlled trial. *J Consult Clin Psychol*. 2023;91(6):350-366. doi:10.1037/ccp0000805

91. Dodds CM, Clark L, Dove A, et al. The dopamine D2 receptor antagonist sulpiride modulates striatal BOLD signal during the manipulation of information in working memory. *Psychopharmacology (Berl)*. 2009;207(1):35-45. doi:10.1007/s00213-009-1634-0

92. Janssen LK, Sescousse G, Hashemi MM, et al. Abnormal modulation of reward versus punishment learning by a dopamine D2-receptor antagonist in pathological gamblers. *Psychopharmacology (Berl)*. 2015;232(18):3345-3353. doi:10.1007/s00213-015-3986-y

93. Määttä JI, Van Den Bosch R, Papadopetraki D, et al. Predicting effects of methylphenidate and sulpiride on brain and cognition: A pharmaco-fMRI, PET study. Design and descriptives. Published online July 27, 2021. doi:10.31219/osf.io/d3h8e

94. Webber HE, Lopez-Gamundi P, Stamatovich SN, De Wit H, Wardle MC. Using pharmacological manipulations to study the role of dopamine in human reward functioning: A review of studies in healthy adults. *Neurosci Biobehav Rev*. 2021;120:123-158. doi:10.1016/j.neubiorev.2020.11.004

## Figure Legends and Captions

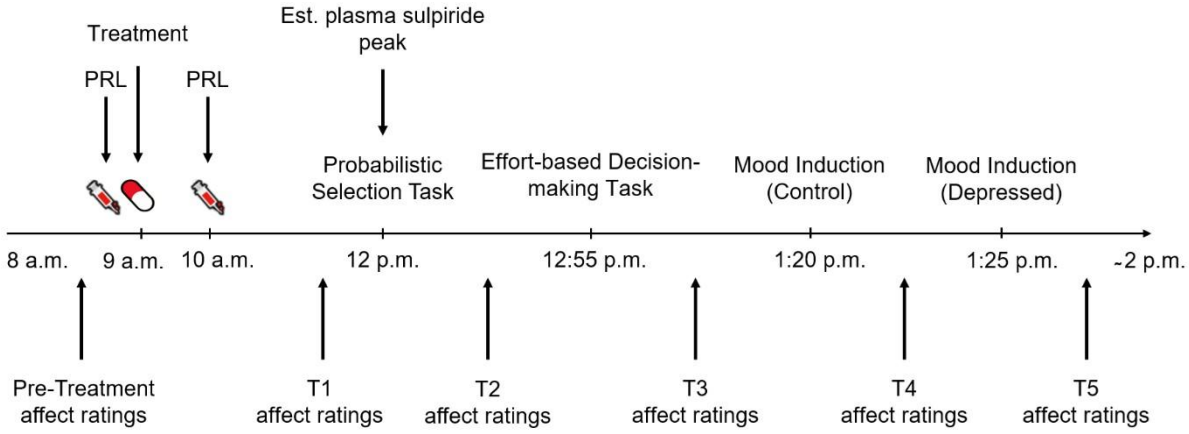


**Figure 1.** *Sequential Illustration of Treatment, Computer Tasks and State Positive Affect*

*Note.* Est. = estimated; PRL = prolactin. Plasma peak of sulpiride was estimated to occur at approximately 3 hours after intake (12 p.m.) when participants underwent the computer tasks.

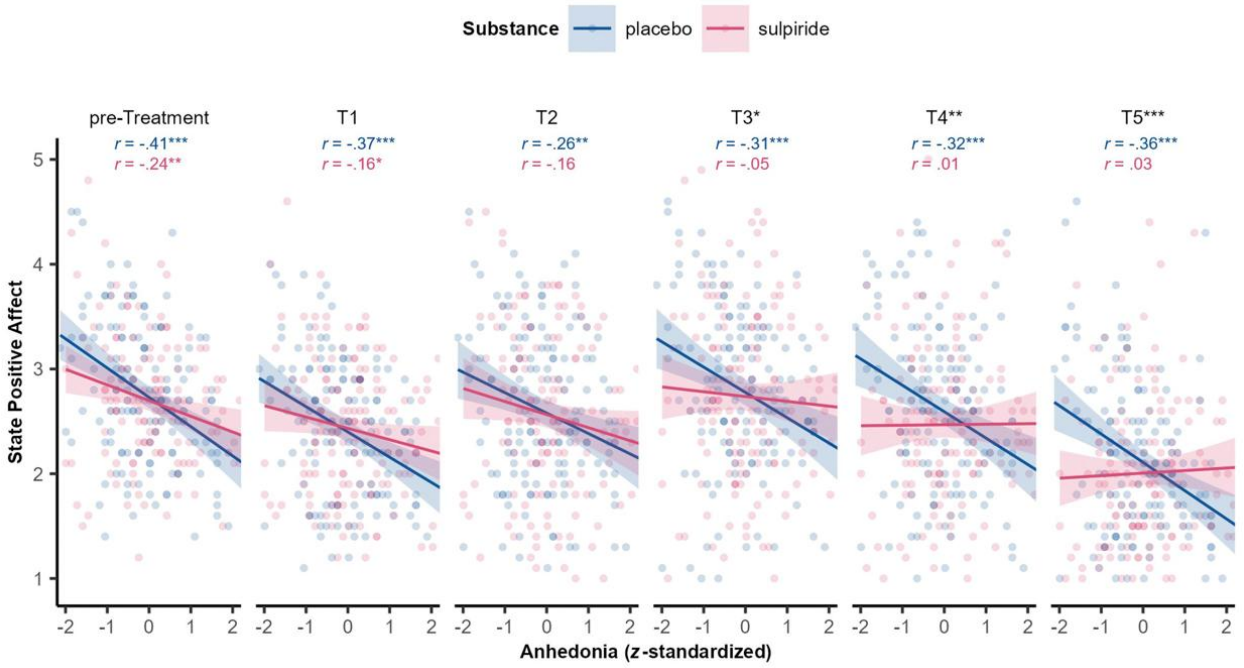


**Figure 2.** *State Positive Affect throughout the Experimental Session Predicted by Substance Groups and Trait Anhedonia*

*Note.* State positive affect via PANAS contrasted with z-standardized baseline trait anhedonia score and separated for substance groups. Black asterisks indicate significantly different correlations. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

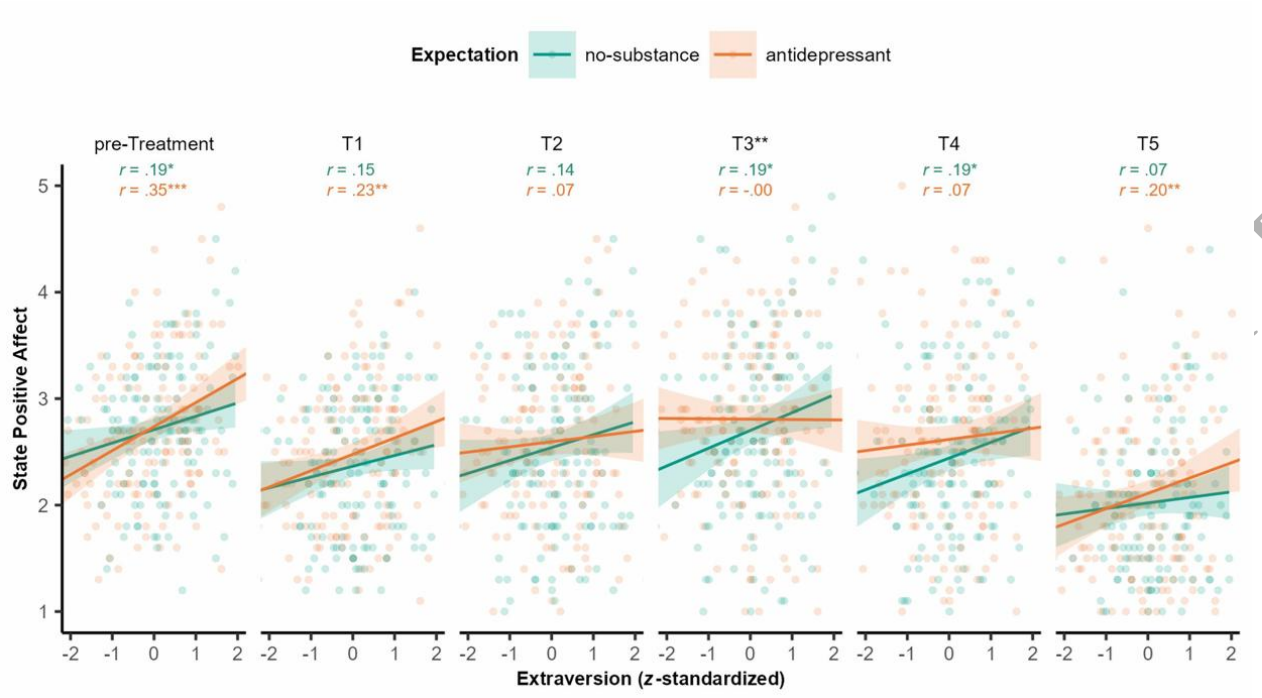


**Figure 3.** *State Positive Affect throughout the Experimental Session Predicted by Expectation Groups and Trait Extraversion*

*Note.* State positive affect via PANAS contrasted with z-standardized baseline trait extraversion score and separated for expectation groups. Black asterisks indicate significantly different correlations. $^{*}p < .05;$ $^{**}p < .01;$ $^{***}p < .001$.

**Table 1**

*Demographic Characteristics at Baseline*

| Baseline characteristic | NS//PLC | | NS//SUL | | AD//PLC | | AD//SUL | | Full sample | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | |
| Female sex | 36 | 49.3 | 37 | 50 | 37 | 51.3 | 37 | 50 | 147 | 50.2 | |
| | M | SD | M | SD | M | SD | M | SD | M | SD | *p* |
| Age | 25.5 | 4.0 | 25.0 | 5.5 | 25.4 | 3.2 | 24.5 | 3.5 | 25.1 | 4.2 | .46 |
| MASQ-D30 Anhedonia | 26.3 | 7.5 | 27.1 | 7.1 | 26.7 | 7.7 | 27.0 | 7.4 | 26.8 | 7.4 | .93 |

*Note.* NS = no-substance expectation; AD = antidepressant expectation; PLC = placebo substance; SUL = sulpiride substance. Participants' sex included either female or male.

**Table 2**

*Results from the Exploratory Factor Analysis of the Related Constructs*

| Scale | Factor loading |
|---|---|
| MASQ-D30 Anhedonic Depression | -.73 |
| SHAPS-D | -.33 |
| BFAS-Extraversion | |
| Enthusiasm | .71 |
| Assertiveness | .55 |
| BDI-II | -.50 |
| TEPS | |
| Consummatory Pleasure | .36 |
| Anticipatory Pleasure | .46 |
| LOT-R | .57 |
| RSTPQ-BAS | |
| Reward Interest | .72 |
| Goal-Drive Persistence | .52 |
| Reward Reactivity | .69 |
| Impulsivity | .47 |
| BIS/BAS | |
| Drive | .54 |
| Fun Seeking | .47 |
| Reward Responsiveness | .69 |
| PVSS | .50 |