The angiotensin antagonist Losartan shifts social reward motivation and punishment feedback sensitivity via modulating midbrain-striato-frontal circuits

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Abstract

Social deficits and dysregulations in dopaminergic midbrain-striato-frontal circuits represent transdiagnostic symptoms across psychiatric disorders. Animal models suggest that modulating interactions between the dopamine and renin-angiotensin system with the angiotensin receptor antagonist Losartan (LT) can modulate learning and reward-related processes. We have therefore determined the behavioral and neural effects of LT on social reward and punishment processing in humans. A pre-registered randomized double-blind placebo-controlled between-subject pharmacological design was combined with a social incentive delay fMRI paradigm during which subjects could avoid social punishment or gain social reward. Healthy volunteers received a single-dose of LT (50mg, n=43) or placebo (n=44). Reaction times and emotional ratings served as behavioral outcomes, on the neural level activation, connectivity and social feedback prediction errors were modelled. Relative to placebo, LT switched reaction times and arousal away from prioritizing punishment towards social reward. On the neural level the LT-enhanced motivational salience of social rewards was accompanied by stronger ventral striatum-prefrontal connectivity during reward anticipation and attenuated activity in the ventral tegmental area (VTA) and associated connectivity with the bilateral insula in response to punishment during the outcome phase. Computational modelling further revealed an LT-enhanced social reward prediction error signal in VTA and dorsal striatum. LT shifted motivational and emotional salience away from social punishment towards social reward via modulating distinct core nodes of the midbrain-striato-frontal circuits. The findings document a modulatory role of the renin-angiotensin system in these circuits and associated social processes, suggesting a promising treatment target to alleviate social dysregulations.

Keywords Losartan, Social reward, Dopamine, Prediction error, Striatum, Ventral tegmental area, Angiotensin-renin system

Introduction

Adaptive processing of social feedback is vital for interpersonal functioning and mental health. Dysregulations in this domain and its underlying neural processes contribute to the development and maintenance of major psychiatric disoders including depression (1-3), social anxiety disorder (4), post-traumatic stress disorder (PTSD) (5), addiction (6), autism spectrum disorder (7, 8), and schizophrenia (9). While these disorders cause tremendous individual suffering and socio-economic costs the development of novel treatments that target social deficits based on the underlying neurobiological dysregulations remains challenging (10, 11).

The Research Domain Criteria (RDoC) framework aims to facilitate novel treatment development by conceptualizing psychiatric disorders from basic dimensions of functioning, including the domains of social communication as well as reward/loss evaluation (12). Together these domains may represent a transdiagnostic treatment target with the potential to improve social functioning. Dysregulations in midbrain-striato-prefrontal circuits have been increasingly established as a core pathogenic mechanism across psychiatric disorders (3, 13-16). Findings from human imaging studies suggest that this circuitry overlaps with that involved in social reward and punishment processing (17, 18) and animal models indicate that neurochemical signalling in this circuitry critically regulates social reward and punishment (19-21). Dopamine (DA) and its interactions with other neurotransmitter systems such as oxytocin play an important role in modulating social reward and punishment in these cicruits (5, 22), however, direct pharmacological modulation of these systems commonly results in negative side effects or highly context-dependent effects, respectively, which critically impede the clinical utility of these approaches (11, 23, 24).

Recent pharmacological studies in healthy humans have demonstrated that targeting the renin-angiotensin system (RAS) via the angiotensin II type 1 receptor (AT1R) antagonist losartan (LT, an approved treatment for hypertension) can modulate reward and threat processing as well as learning and memory in the absence of negative side effects (25-29). Earlier animal models suggest an interaction between the RAS and the central DA system, including a dense expression of RAS receptors in midbrain-striato-prefrontal circuits (30) and functionally significant angiotensin II receptors located presynaptically on dopaminergic neurons (31, 32). LT induced concentration-dependent inhibition of dopamine release via inactivation of AT1R (33), but also enhanced dopamine D1 receptor (D1R) signaling which may contribute to both its effects on hypertension (34) and reward-related processes (35, 36). Additionally, optogenetic inhibition/activation of ventral tegmental area (VTA) dopaminergic neurons - which exhibit dense AT1R expression - revealed that cue-evoked DA release accurately encodes reward prediction errors (37, 38), thus supporting behavioral adaptation and associative learning (39, 40). Together, the available evidence suggests that targeting the RAS via LT may represent a promising candidate to modulate neural processing in midbrain-striatal-prefrontal circuits which critically mediate flexible behavioral adaption in the domains of feedback-dependent learning as well as earlier stages of social and non-social reward processing (17, 18,

22, 41, 42). Initial evidence for the functional and behavioral relevance of this strategy in humans comes from a recent study that demonstrated that a single dose of 50mg LT can modulate feedback-dependent learning in healthy individuals such that LT enhanced the difference between loss and reward feedback learning rates and suppressed loss learning rates (29). Determining behavioral and neural effects on earlier stages of reward and punishment processing in social contexts will facilitate a translational neuroimaging approach which facilitates both translation from animal models, indicating that RAS-DA interactions modulate reward-related processing in these cicruits (19, 20, 35, 36), and translation into therapeutic application in populations with social deficits.

Reward-related neural responses in this circuitry encompass anticipatory and consummatory signals, closely linked to brain activation in the midbrain-striatal-frontal circuit, particularly the VTA, striatum, and frontal cortex (17, 18, 22). From a computational modelling framework, prediction error (PE) signals critically rely on DA-dependent signaling in these areas (43), although the prediction error is not limited to reward and punishment processing but also includes sensory-perceptual processes as well as higher order processes such as social learning (43-45).

Against this background we combined a pre-registered randomized double-blind between-group placebo-controlled pharmacological experiment with functional MRI (fMRI) and computational modelling to examine whether social reward and punishment processing can be modulated by a single dose of LT, thus bridging the translational gap between animal model and human research as well as to determine the clinical potential of LT. To this end healthy volunteers (n = 87) underwent a well-validated social incentive delay (SID) fMRI paradigm (5). Behavioral indices reflecting motivation and subsequent emotional impact of social feedback, neural indices during reward and punishment anticipation and outcome, as well as social feedback PE signalling served as primary outcomes. Based on findings from animal and human studies we hypothesized that LT would (a) enhance differential processing of reward and punishment on the behavioral level (29), which on the neural level would be reflected in (b) enhanced differential activiation and connectivity in VTA-striatal-frontal circuits during social reward-punishment processing, and (c) enhance social feedback PE signalling during the outcome phase.

Materials and method

Participants

Ninety healthy participants (age range 18-27 years) were recruited via advertisements for the randomized placebo-controlled between-subject pharmacological fMRI study which encompassed a single-dose p.o. administration of 50mg LT or placebo (PLC) and subsequent administration of a social incentive delay fMRI paradigm (SID) with a demonstrated sensitivity to capture pharmacological modulations (adopted from Nawijn, van Zuiden (5)). Exclusion criteria included color blindness; systolic/diastolic blood pressure > 130/90 mmHg or < 90/60 mmHg; current or regular substance or medication use; current or history of medical or psychiatric disorders; any endocrinological abnormalities or contraindications for LT administration and MRI.

Participants were asked to abstain from caffeinated drinks on the day of the assessment (e.g., coffee, tea, energy beverages). Two participants were excluded because their baseline blood pressure was outside our predefined criteria, one participant was excluded due to technical failiure during MRI acquisition leading to a final sample of N = 87 (N = 43, 26 males, LT; N = 44, 24 males, PLC) included in all subsequent analyses (details see **Table 1**).

Pharmacological and experimental procedure

Participants were stratified for sex and randomly allocated to treatment in a double-blind design. Treatment was packed in identical capsules, counterbalanced across sexes and dispensed by an independent researcher. To reduce potential confounding effects of early life stress (46), impulsiveness, sensitivity to punishment and reward on reward-related neural processing the Childhood Trauma Questionnaire (CTQ), Barratt Impulsiveness Scale (BIS), and Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) were administered at baseline (**Figure 1A**) (47-49). Given that after oral administration LT peak plasma levels are reached after 90 minutes with a terminal elimination half-life ranging from 1.5 to 2.5 hours (50-52) the experimental paradigm started 90 minutes after treatment (in line with (26, 53)). LT rapidly crosses the blood-brain barrier (54, 55) and while effects at central receptors have been observed after 30 minutes after i.e. administration effects on cardiovascular indices only become apparent after 3 hours (e.g. (50) , see also (26, 29)). To further control for potential confounding effects of LT on cardiovascular activity blood pressure and heart rate were assessed before drug administration, as well as before and after the fMRI paradigm (**Figure 1A**). To control for nonspecific affective effects of LT the affective state of participants was tracked troughout the experiment via the Spielberger State–Trait Anxiety Inventory (STAI) and the Positive and Negative Affective Scale (PANAS) which were administered before drug administration, at the time of peak plasma concentrations and after the experiment (56, 57) (**Figure 1A**). The subsequent affective impact of LT-induced changes on social feedback processing was assessed via ratings of the cues before treatment, after fMRI, and following feedback stimuli after fMRI (**Figure 1A**). After the entire experiment participants were asked to guess the treatment they received.

Written informed consent was obtained from each participant before enrollment, the study was approved by the local institutional ethics committee, all procedure followed the Declaration of Helsinki, and the study was preregistered as clinical trial (registration number: NCT04604756, URL: https://clinicaltrials.gov/ct2/show/NCT04604756).

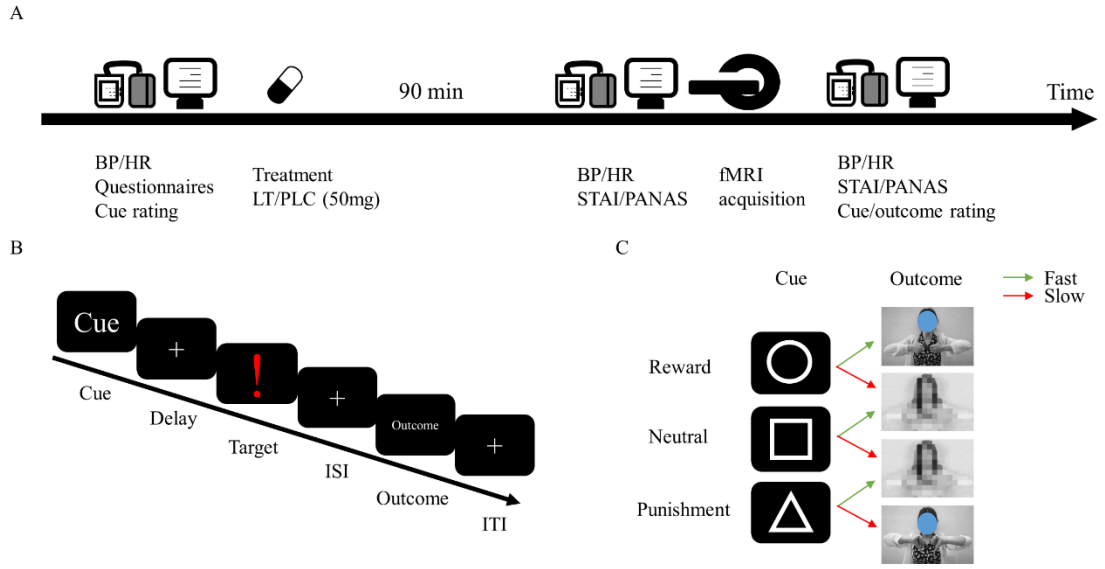

Figure 1. Schematic depiction of the experimental protocols and the experimental paradigm. (A) The entire experimental procedure encompassed baseline assessment, drug administration, assessments before fMRI (corresponding to estimated peak plasma levels) and post fMRI acquisition. Abbreviations: BP = blood pressure, HR = heart rate, LT = losartan, PLC = placebo, STAI = state-trait anxiety inventory, PANAS = positive and negative affect schedule. (B) Schematic representation of the trial structure in the SID paradigm. Each trial started with a 500ms cue presentation (circle, reward trial; square, neutral trials, and triangle, punishment trials) followed by a delay (jittered between 1000 and 3000 ms). Next the target appeared with a duration adjusted to the individual response time. After an inter-stimulus interval (ISI, 2000 ms – target duration) the outcome was presented for 1500 ms, followed by an inter-trial interval (ITI) with a duration jittered between 1000 and 3000 ms. (C) Cues and corresponding outcomes (for display only) per trial type. Social reward feedback was shown in response to fast reactions on reward trails, social punishment feedback was shown in response to slow reactions on punishment trials. Note that for the preprint version the face was overlayed by a blue oval.

Social incentive delay task

We employed a validated social incentive delay (SID) task-fMRI paradigm with a demonstrated sentivity for pharmacological manipulations (adopted from Nawijn, van Zuiden (5)). Briefly, the paradigm presents condition-specific cues (positive, negative, neutral) which signal that a social reward can be obtained or a social punishment can be avoided (anticipation). Next, participantss undergo a reaction time task which is followed by the presentation of a performance-dependent social reward, punishment or neutral feedback (outcome) (**Figure 1B**). Participants received task instructions and a practice session prior to the formal experiment. During the paradigm 27 trials for reward and punishment conditions, and 18 trials for the neutral condition were presented (pseudo-randomized). Each trial started with presentation of a geometric cue indicating the trial type (circle: reward, triangle: punishment, and square: neutral, **Figure 1C**). After a delay, the target was presented in the center of screen and participants were required to press a button as fast as possible. Responses within target presentation time represented hits while omissions or responses outside of

target presentation time represented misses. To facilitate a sufficient number of trials for each outcome condition an adaptive performance algorithm was employed. To this end, trial-wise reaction times (RT) were recorded and employed to adjust the duration of the next target presentation to individual performance. By increasing or decreasing target durations, 66.7% of reward-cue and punishment-cue trials were followed by social reward or punishment, respectively. This resulted in a performance-dependent sufficient number of reward (hit) feedback trials (±18) and punishment (miss) feedback trials (±18) for further analyses. The target was followed by an adaptive inter-trial-interval and presentation of the condition- and performance-dependent outcome. In the social reward condition hits resulted in rewarding social feedback, i.e. a smiling person in thumbs-up pose, while misses resulted in neutral feedback, i.e. scrambled picture of the person. In the social punishment condition hits allowed avoidance of social punishment (neutral feedback), while misses resulted in social punishment feedback, i.e. a person with a contemptuous look in thumbs-down pose. For neutral trials both, hits and misses resulted in neutral feedback. The experimental materials for the outcome were initially collected and rated by an independent sample. To further explore the subsequent emotional effects of the paradigm participants rated perceived arousal, likeability, dislikeability, intensity, valence of cues and outcomes on a 9-point Likert scale after the fMRI session (**Figure 1A**).

Behavioral analysis

To maintain the trial-specific information of the SID task and increase sensitivity, a linear mixed model was used with condition (social reward, punishment, neutral) and treatment (LT, PLC) as two fixed factors and subject as random factor to account for individual adaptations of reaction time windows. Trials with no responses and RTs ±3SD on the individual level were removed. Treatment effects on emotional perception ratings of cues and outcomes were examined with separate ANOVA and liner mixed models (see **supplementary method**).

MRI data acquisition and preprocessing

MRI data was acquired using a 3.0 Tesla GE MR750 system (General Electric Medical System, Milwaukee, WI, USA). Preprocessing was fully implemented in fMRIPrep (58) except for smoothing with a Gaussian kernel at full width at half maximum (FWHM, 8 × 8 × 8 mm) conducted in SPM12 (Welcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ac.uk/spm/software/spm12) (59). Details please see **supplementary method**.

Individual- and group-level BOLD level fMRI analyses

On the first-level the SID task was modeled employing the hemodynamic response function (HRF) and corresponding derivatives on the onsets of the experimental conditions, i.e. cue, target, and outcome. The three different types of anticipation were modeled according to the cues signaling a potential social reward, social punishment, and neutral outcome. In line with previous studies the cue and subsequent delay were modelled as anticipation period (2, 60-62). In line with the potential response pattern

of the participants five different types of outcome were modeled, including reward or neutral feedback in reward trial, punishment or neutral feedback in punishment trial, and neutral feedback in neutral trial. Additional confound regressors included target responses and head motion as defined by six rigid movement parameters from the motion correction. On the group level effects of treatment were examined employing mixed ANOVA analyses with the factors (condition, treatment) for each phase. Based on our a priori regional hypotheses the analyses focused on the ventral striatum (VS), dorsal striatum (DS) (63) and VTA (64) as Regions of Interest (ROIs).

Functional Connectivity Analysis

To determine the social reward-punishment networks we initially examined neural activity during receipt of feedback [reward + punishment – neutral] in the entire sample. Results revealed that social feedback induced stronger activity in regions involved in salience, value and social processes, including insula, striatum, dorsal medial prefrontal cortex (dmPFC), and occipital lobe (**Figure S1C**). Combined with the a priori defined VTA-striatal structural maks three peak coordinates (VS: [22, -6, -10], DS: [-14, -2, -8], VTA: [10, -14, -12]) were identified to construct spherical seeds with 6 mm radius which served as seeds for the generalized psychophysiological interactions (gPPI) analysis (65) (**supplementary method**). Treatment effects were determined by comparing the seed-region-specific connectivity maps by means of mixed ANOVA analyses with the factors (condition, treatment) on the whole brain level (separately for each phase). To further disentangle significant interaction effects parameter estimates were extracted from regions exhibiting significant interaction effects involving treatment.

Computational modelling of social feedback prediction errors on the neural level

Due to the consistent information carried by cue and outcome in neutral condition, the prediction error for each trial was only computed for the social reward and social punishment conditions and employed as a trial-wise parametric modulator on the neural level (66). The prediction error (PE) and expected value (EV) for each trial were estimated based on the Rescorla-Wagner model (66-68). The value estimation was based on the equations:

$$PE_t = R_t - EV_t$$
$$EV_{t+1} = EV_t + \alpha \times PE_t$$

PE reflects the difference between the expectation and the actual outcome, and EV reflects the expectation of receiving a certain feedback on a given trail. R is the actual feedback received, t is the given trial, and α is the learning rate. The initial EV for social reward anticipation and social punishment anticipation were set up with 0.5 and -0.5 respectively. In line with previous studies (66, 69) a learning rate α = 0.7 was used across participants. The EV for the next trial is updated based on the EV of the current trial and the prediction error of that trial multiplied by the learning rate. Since previous studies show that a wide range of learning rates (0.2 to 0.7) do not affect the computation (66, 67, 69-71), an additional test was conducted by calculating at a

learning rate of 0.2, which confirmed that changing the learning rate did not affect our main findings (see **supplementary results**).

For determining the social feedback PE on the neural level EV and PE were included in the first level GLM models as parameter modulations corresponding to anticipation and outcome phase respectively. On the first level the GLM models corresponded to the BOLD activation models and the the expectation value and prediction error from the computational model were added into the first-level model as additional parameter modulations for the anticipation and outcome respectively. Based on previous studies (66, 69) outcome stage was modeled without taking specific feedback into account to avoid overfitting. Treatment effects on the second level were examined by means of directly comparing the two treatment groups by means of independent t tests.

Thresholding

ROI analyses were conducted in the R package 'afex', and the statistical significance level set to $p < .05$. On the whole-brain level an tinitial cluster-forming threshold was set to voxel level $p < .001$, and statistical significance was determined via cluster-level inference and familywise error (FWE) control for multiple comparisons with $p_{FWE} < .05$ (72).

Results

Participants

Treatmemnt groups (losartan, n = 43; placebo, n = 44) exhibited comparable sociodemographic and psychometric characteristics (**Table 1**). During the experiment no differences in baseline assessments or changes in heart rate, blood pressure, and emotional state were observed between the treatment groups and total guess accuracy was 52.87% together arguing against the impact of potential confounders and unspecific effects of LT.

Table 1. Participant Demographics and Control Measures

Characteristic	Time	**LT**, N = 43	**PLC**, N = 44	Statistic	*p* value
Age, years		21.56 (2.29)	20.84 (1.94)	1.6	0.119
Sex				0.12	0.733
Male		26 (60%)	24 (55%)		
Female		17 (40%)	20 (45%)		
Body mass index, kg/m^2		21.02 (2.38)	21.33 (3.35)	-0.49	0.622
CTQ		36.81 (7.89)	34.59 (5.36)	1.5	0.129
BIS- AI		14.35 (2.91)	14.18 (2.31)	0.30	0.768
BIS- MI		22.84 (3.73)	22.11 (3.95)	0.88	0.382
BIS- NPI		23.65 (4.23)	23.55 (4.09)	0.12	0.906

SPSR- SP		24.40 (4.58)	25.20 (3.52)	-0.92	0.359
SPSR- SR		23.02 (2.51)	22.48 (3.37)	0.86	0.393
Systolic blood pressure	Baseline	116.42 (7.60)	114.55 (9.01)	1.0	0.297
	Before MRI	110.26 (8.94)	110.18 (9.64)	0.04	0.970
	After MRI	115.40 (8.12)	112.98 (9.80)	1.3	0.213
Diastolic blood pressure	Baseline	72.42 (6.59)	70.89 (6.93)	1.1	0.294
	Before MRI	69.16 (6.83)	67.61 (6.21)	1.1	0.272
	After MRI	71.67 (6.38)	70.18 (8.12)	1.0	0.342
Heart rate	Baseline	80.05 (12.50)	76.05 (11.31)	1.6	0.121
	Before MRI	70.84 (11.23)	69.73 (8.36)	0.52	0.603
	After MRI	69.70 (11.29)	71.52 (11.44)	-0.75	0.456
PANAS- negative affect	Baseline	16.58 (4.99)	15.57 (4.41)	1.0	0.319
	Before MRI	14.68 (4.67)	13.73 (3.82)	1.0	0.323
	After MRI	13.82 (4.37)	13.74 (4.89)	0.08	0.932
PANAS- positive affect	Baseline	27.16 (5.97)	26.77 (5.51)	0.32	0.752
	Before MRI	25.88 (6.38)	24.93 (5.55)	0.71	0.478
	After MRI	24.68 (7.02)	24.67 (5.93)	0.01	0.995
STAI- state anxiety	Baseline	38.98 (7.27)	39.41 (6.84)	-0.29	0.776
	Before MRI	38.50 (7.57)	38.78 (7.87)	-0.16	0.870
	After MRI	38.92 (8.67)	38.86 (8.05)	0.04	0.971
STAI- trait anxiety	Baseline	41.35 (8.16)	40.82 (7.71)	0.31	0.756
	Before MRI	40.65 (7.74)	40.54 (7.75)	0.07	0.948
	After MRI	40.58 (8.32)	41.00 (8.23)	-0.23	0.817

[a] Descriptive statistics: mean (SD); n (%)

[b] Statistical tests: Welch Two Sample t-test; Pearson's Chi-squared test

[c] LT = losartan, PLC = placebo, PANAS = Positive and Negative Affect Schedule, STAI = Spielberger State-Trait Anxiety Inventory, CTQ = Childhood Trauma Questionnaire, BIS = Barratt Impulsiveness Scale (AI = attentional impulsiveness, MI = motor impulsiveness, NPI = non-planning impulsiveness), SPSR = Sensitivity to Punishment and Sensitivity to Reward questionnaire (SP = sensitivity to punishment, SR = sensitivity to reward)

[d] Due to technological issues of PANAS and STAI assessments 3 recordings in LT group and 2 recordings in PLC group were lost during before and after MRI phases.

Losartan and experimental effects on motivational significance and affective evaluation

The linear mixed model revealed a significant interaction effect ($F = 3.706$, $p = 0.025$, **Figure 2A**) between condition and treatment on reaction times indicating that LT induced significantly stronger differences between social punishment vs social reward as compared to PLC ($t = 2.679$, $p = 0.007$), reflecting a shift in the approach-

avoidance motivation of social feedback. The main effects of treatment and condition were not significant.

Examining effects of the experimental manipulation and treatment on the affective evaluation by means of a linear mixed model revealed a significant condition main ($F = 404.983$, $p < 0.0001$, **Figure 2B**) and condition times treatment interaction effect ($F = 4.914$, $p = 0.007$) on arousal ratings for outcomes. Post hoc analyses showed that LT increased the reward-punishment difference ($t = 2.390$, $p = 0.017$) and decreased punishment-neutral difference ($t = -2.952$, $p = 0.003$) relative to PLC. With respect to dislikeability ratings for the outcomes a linear mixed model revealed significant condition main ($F = 633.848$, $p < 0.0001$, **Figure 2C**), and condition times treatment interaction effects ($F = 3.413$, $p = 0.033$). Post hoc tests showed that LT increased the punishment-neutral difference ($t = 2.597$, $p = 0.0095$) relative to PLC. No significant treatment main or interaction effects were observed on cue or other outcome ratings (see **supplementary results**).

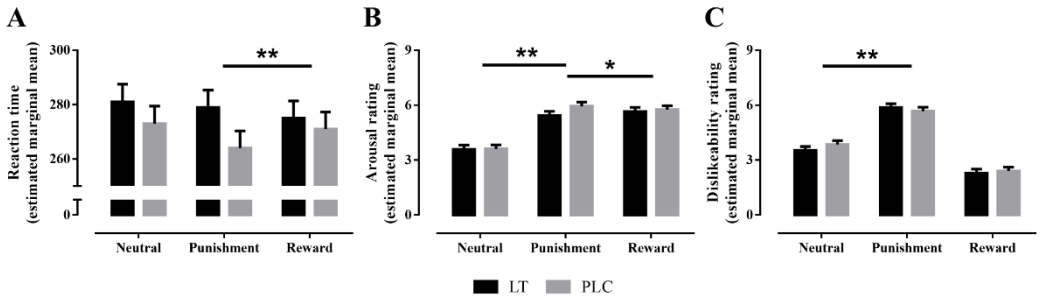

Figure 2. Reaction time, arousal and dislikeability ratings of the feedback pictures presented during outcome. Estimated marginal mean and stand error of reaction time (A), arousal rating (B), and dislikeability rating (C) are presented. * and ** denote relevant significant post hoc differences at $p < 0.05$ and $p < 0.01$ respectively. LT = losartan, PLC = placebo.

Losartan effects on neural activation during anticipation phase

No significant main or interaction effects of treatment were observed in the a priori ROI analyses on extracted parameter estimated from the VTA (treatment, $F = 2.67$, $p = 0.106$; interaction, $F = 0.309$, $p = 0.724$), VS (treatment, $F = 1.277$, $p = 0.2616$; interaction, $F = 0.218$, $p = 0.7802$), and DS (treatment, $F = 0.96$, $p = 0.33$; interaction, $F = 0.65$, $p = 0.5165$). In addition an exploratory whole-brain analysis confirmed the lack of significant treatment main and interaction effects (at $p_{FWE} < 0.05$). Significant main effects of condition during the anticipation phase are provided in **supplementary results** (**Figure S1A**, **Table S1**).

Losartan effects on neural activation during outcome phase

The ROI analysis revealed a significant treatment times condition effect on the VTA ($F = 3.24$, $p = 0.0435$), reflecting that LT significantly increased the difference between reward and neutral ($t = 2.407$, $p = 0.0172$) as well as between reward and punishment ($t = 1.924$, $p = 0.056$, marginal significant). The exploratory whole-brain analysis did not reveal further regions exhibiting treatment effects suggesting highly

specific regional effects of LT. Significant main effects of condition during the anticipation phase are provided in **supplementary results** (**Figure S1B, Table S1**).

Losartan effects on the network level

On the network level significant interaction effects between condition and treatment were found for the VS during anticipation but for the VTA during the outcome phase (all findings passed whole-brain $p_{FWE} < .05$, **Figure 3**, **Table 2**). Subsequent post-hoc tests revealed that LT significantly modulated VS-middle frontal gyrus (MFG) connectivity during neutral-punishment ($t = 2.541$, $p = 0.0119$), punishment-reward ($t = -3.910$, $p = 0.0001$), and between social reward feedback ($t = 2.451$, $p = 0.0151$) processes, with the effects being driven by enhanced coupling during social reward-anticipation. In contrast, LT specifically modulated VTA-networks during outcome, such that LT modulated VTA-insula (left) connectivity during the neutral-punishment pattern ($t = 2.613$, $p = 0.0098$), the punishment-reward pattern ($t = -4.671$, $p < 0.0001$), the neutral-reward pattern ($t = -2.059$, $p = 0.0410$), and within social punishment ($t = -2.012$, $p = 0.0456$) and social reward ($t = 3.128$, $p = 0.002$) respectively. In addition, LT modulated both VTA-insula (right) and VTA-SFG connectivity for neutral-punishment($t = 5.023$, $p < 0.0001$; $t = -3.127$, $p = 0.0021$) and punishment-reward patterns ($t = -3.683$, $p = 0.0003$; $t = 4.368$, $p < 0.0001$, **Figure 3C**). Losartan also changed VTA-insula (right) connectivity in social punishment ($t = -2.512$, $p = 0.0128$) and neutral ($t = 3.13$, $p = 0.002$), VTA- superior frontal gyrus (SFG) connectivity in social punishment ($t = 3.613$, $p = 0.0004$). A direct comparion between treatments revealed consistent effects of LT on processing of social punishment feedback, such that it decreased VTA communication with the bilateral insula, yet enhanced VTA communication with the SFG.

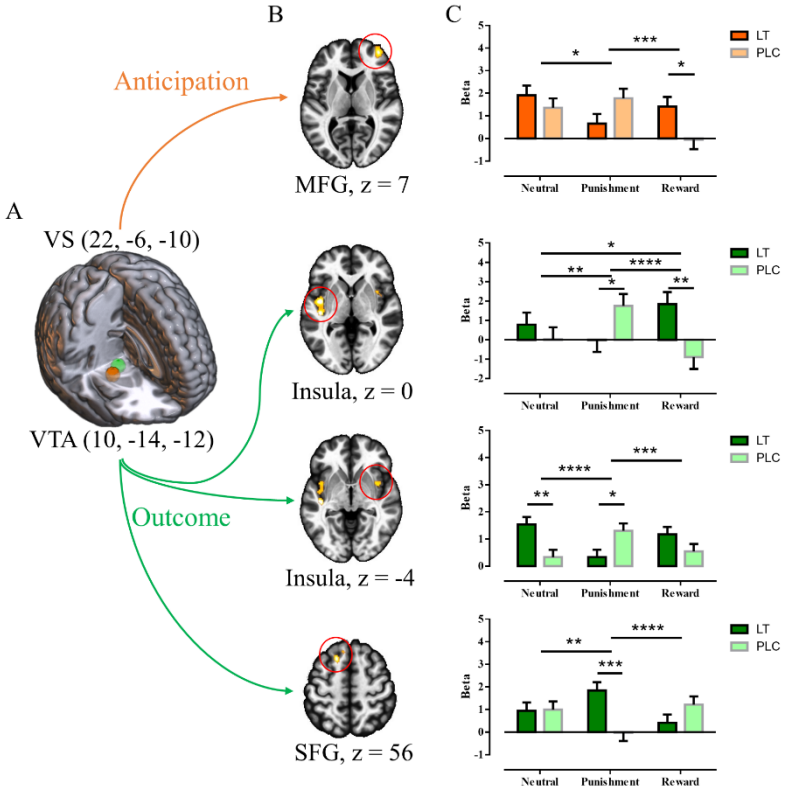

Figure 3. Effects of LT on the network level. (A) Seeds of interest, i.e. VS and VTA. (B) Regions exhibiting significant conditions times treatment interaction effects during anticipation and outcome phases. (C) Post hoc tests on extracted parameters from each significant clusters. VS = ventral striatum VTA = ventral tegmental area, SFG = superior frontal gyrus, MFG = middle frontal gyrus, LT = losartan, PLC = placebo, *, **, ***, and **** denote relevant significant post hoc differences at $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$ respectively.

Table 2 Functional connectivity results

Cluster region	Cluster size	x	y	z	*F* value
Anticipation phase, VS seed					
MFG	309	38	56	8	13.69
		38	60	16	11.41
Outcome phase, VTA seed					
L insula, STG	427	-44	-22	-2	15.16
		-44	-6	0	12.50
		-40	6	-6	10.44
R insula, putamen	246	40	12	16	14.09
		38	4	-6	11.07
		30	12	10	10.93
SFG	213	-18	20	56	11.75
		-8	30	60	9.83
		-30	22	46	8.26

Note: All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$. L = left, R = right, SFG = superior frontal gyrus, MFG = middle frontal gyrus, STG = superior temporal gyrus.

Losartan effects on the social feedback prediction error

The ROI analysis indicated that LT significantly enhanced the social feedback PE in DS ($t = 2.454$, $p = 0.0162$) and VTA ($t = 2.227$, $p = 0.0286$) but not the VS ($t = 1.264$, $p = 0.2098$) compared to PLC (**Figure 4**). Further exploratory whole brain analysis revealed both significant positive and negative social feedback PE modulation in widespread subcortical-cortical networks (**Figure 5A & 5B**, **Table 3**), while LT enhanced the social feedback PE in a cortical midline and superior temporal network encompassing the precuneus, STG, SFG, MFG, cingulate gyrus and SMA (**Figure 5C, Table 3**).

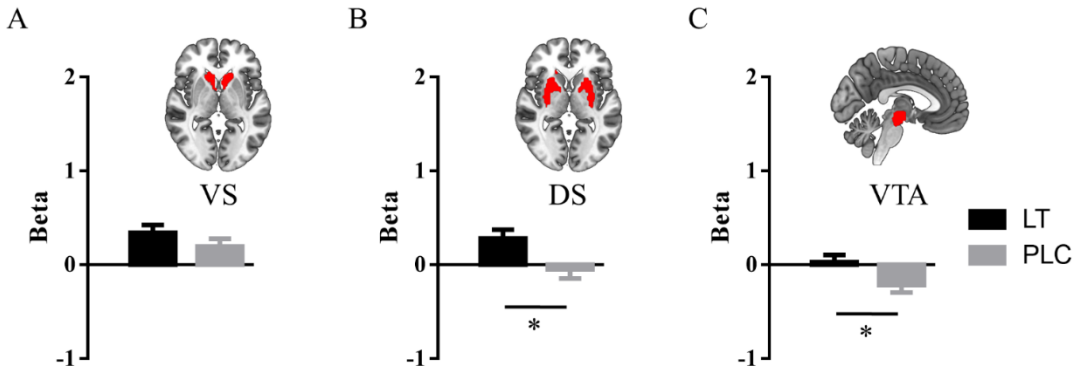

Figure 4. Parameter estimates reflecting extracted neural PE signals from the corresponding midbrain and striatal regions. * denote relevant significant post hoc differences at $p < 0.05$. VS = ventral striatum, DS = dorsal striatum, VTA = ventral tegament area, LT = losartan, PLC = placebo.

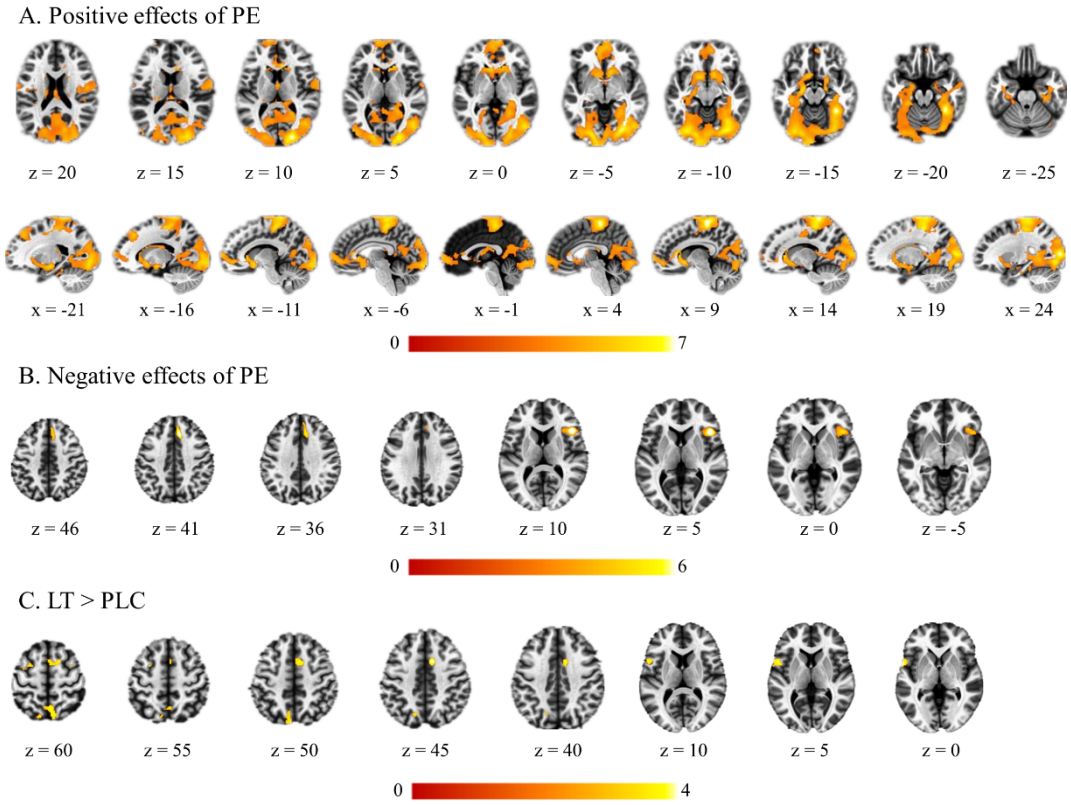

Figure 5. Prediction error (PE) related neural signals. (A) Positive effects of PE, (B) negative effects of PE, and (C) regions exhibiting an enhanced PE by losartan compared to placebo. All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$. LT = losartan, PLC = placebo.

Table 3 Neural correlates of prediction error

Cluster region	Cluster size	x	y	z	*t* value
Positive effects of PE					
Parietal Lobe, mPFC, SFG, Precuneus	12731	8	-30	66	8.13
		14	-38	74	7.22
		20	-34	56	6.83
Occipital Lobe, Temporal Lobe, subcortical regions*	28095	36	-48	-16	7.92
		24	-92	8	7.21
		32	-80	-8	7.12
vmPFC, SFG, MFG, mPFC	733	-18	34	44	5.36
		-24	20	32	3.84
Negative effects of PE					
IFG, insula	707	46	20	8	6.47
		36	26	-4	4.37
		32	22	12	4.05
mPFC, cingulate gyrus	417	8	28	40	5.42
		10	38	26	3.87
		6	44	38	3.62
LT > PLC					

SFG, MFG, cingulate gyrus, SMA	1891	12	-4	76	5.09
		-18	-16	78	4.94
		28	-4	68	4.19
STG	316	-60	6	0	4.25
		-54	10	8	4.08
		-56	6	18	3.24
Precuneus	728	10	-66	64	4.05
		-16	-70	44	3.79
		-6	-82	52	3.79

Note: All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$. LT = losartan, PLC = placebo, IFG = inferior frontal gyrus, SFG = superior frontal gyrus, mPFC = medial prefrontal cortex, vmPFC = ventral medial prefrontal cortex, MFG = middle frontal gyrus, STG = superior temporal gyrus, MTG = middle temporal gyrus, SMA = supplementary motor area. * parahippocampal gyrus, caudate, putamen, amygdala, thalamus.

Exploratory analyses of sex-differences

Potential sexual dimorphic effects of LT were examined in exploratory analyses encompassing the factor sex. No sex-differences were observed, except for a stronger LT effect on the striatal PE in men (**supplementary results**).

Discussion

The present pharmacological fMRI trial aimed to determine whether targeting the RAS system via LT can modulate social reward and punishment processing via modulating VTA-striatal-frontal circuits. On the behavioral level LT modulated the motivational significance of social reward and punishment during anticipation while affecting the subsequent affective evaluation of social stimuli. On the neural level the enhanced motivational significance was reflected by increased coupling between the VS and MFG during anticipation of social rewards. During the outcome phase LT enhanced neural signals in the VTA and associated prediction error signals in VTA and DS while attenuating VTA-insula communication and concomitantly enhancing VTA-SFG communication during social punishment. Together, these findings provide a potential mechanism by which LT may enhance social reward motivation while decreasing social punishment sensitivity.

On the behavioral level LT shifted the motivational significance and arousal experience for social punishment relative to social reward feedback, an effect that was mainly driven by prolonged reaction times during anticipation of and subsequently reduced arousal reaction towards social punishment stimuli. These findings partly align with observations in previous studies, such that following LT healthy subjects perceived loss outcomes as being less informative resulting in an attenuated loss learning rate (29), and exhibited accelerated extinction and autonomous arousal decreases towards threat (26). Together, these observations indicate that LT may attenuate the impact of negative information thus shifting anticipatory motivation and post encounter learning towards positive information.

On the neural level the relative motivational shift between negative and positive social information was accompanied by a modulation of VS-frontal circuits, such that LT reduced VS-MFG connectivity during anticipation of social punishment but increased connectivity in this circuit during anticipation of social reward. Convergent evidence suggests that the VS plays a key role in dopamine-mediated anticipatory and motivational processes (17, 18, 42) and that the pathways between the VS and frontal regions are critically involved in associated social processes including motivational and reinforcing aspects of social interactions (73, 74). In patients with marked social impairments pharmacological modulation of the coupling between VS and MFG has been associated with improved computation of future positive social outcomes (75, 76) and effects on this circuit may thus reflect a potential mechanism via which LT can increase social motivation.

In contrast to the modulation of VS-centered circuits during the anticipation stage, LT specifically modulated VTA activity as well as its connectivity with insular and frontal regions during the outcome phase. During the social feedback presentation stage LT increased the differential processing of rewarding feedback from both, negative as well as neutral feedback in the VTA. The VTA represents a pivotal node in dopamine-modulated reward processing and learning circuits (17, 22, 40, 77) and together with the amygdala drives dopaminergic signaling in response to social stimuli (22, 74), suggesting that LT rendered positive social signals as more salient. In contrast, LT specifically decreased coupling of the VTA with the bilateral mid-posterior insula in response to social punishment. The insula plays a key role in salience and interoceptive information processing, with the mid-posterior insula being involved in representing the intensity of aversive experiences (78, 79). This suggests that LT may have attenuated the aversive emotional impact of negative social feedback on the insula leading to lower arousal ratings for the negative social stimuli following the experiment.

We further combined a computational modeling framework to determine effects of LT on the neural social prediction error i.e. the difference between expected and actual social feedback. The feedback evoked PE signal is a closely linked to the dopamine transmission based neural teaching signal and thus promotes behavioral adaptations to the external environment (38, 39, 44). LT enhanced the social feedback PE signal on the neural level in the VTA and DS and convergent evidence suggest that the PE signal is strongly influenced by dopaminergic signalling. Previous animal models suggest interactions between the RAS and the DA system, such that LT activiated D1R (34) and inhibited DA release (32, 33) in these circuits, which may suggest that LT enhanced PE encoding in these regions via effects on DA neurons rather than on postsynaptic dopaminergic transmission. In addition, LT also enhanced PE signaling in other regions, including frontal and superior temporal areas as well as the precuneus. Whereas RPE signals have been mostly examined in midbrain and striatal regions, accumulating evidence suggests that depending on the specific domains and context more extended networks encompassing limbic, frontal and parietal regions are involved (43, 44). For instance, the concommitant engagement of the mPFC, amygdala, hippocampus with the precuneus and the default network has

been proposed to play a key role in initiating and maintaining exploratory and exploitative behavior (45, 77, 80), while the insula has been strongly associated with negative PEs signaling sensitivity to punishment (24, 81, 82). The regions affected by LT encompass onesinvolved in executive functions and social processes such as self referential processing and theory of mind (80) suggesting that LT in the present context may have modulated not only reward-related PE signals but also other components of the PE.

From a functional neuroanatomy perspective LT modulated neural activity and connectivity of distinct key nodes of the midbrain-striatal system during different aspects of social feedback processing. Thus, VS connectivity was specifically affected during anticipation while VTA networks and VTA/DS PE signaling were modulated during the outcome phase. This dissociation aligns with the distinct functions of these core nodes in feedback-associated social and non-social processes (63, 83, 84). The VTA encompasses the majority of dopaminergic cell bodies and is strongly involved in predicting outcomes including social error signals and guiding flexible adaptation (17, 22, 46, 85), whereas the VS which receives dopaminergic projections from the VTA, is strongly involved in appetitive motivation and reward-expectation for both social and non-social feedback (17, 18) while the DS is stronger involved in learning, action initiation, and habit formation (16, 83). Altough most of these functions encompass social as well as non-social processes their critical role in reward and punishment processing critically influences social behavior (45, 73, 74). The process-specific effects of LT on distinct nodes may reflect that the RAS plays a complex role in regulating social reward and punishment processes.

Social deficits such as decreased social motivation or a hypersensitivity to social punishment represent a core symptom across several mental disoders including depression (2, 3), social anxiety disorder (4), post-traumatic stress disorder (5, 15), autism spectrum disorder (7, 8), and schizophrenia (9). Together with accumulating evidence from previous studies (26, 27, 29) our findings suggest that LT may have a promising potential to enhance social motivation to obtain rewards while decreasing sensitivity to punishment in social contexts and attenuate these dysregulations in patient populations.

Although the current study employed a strict pre-registered and randomized-controlled design the findings and interpretation need to be considered in the context of the following limitations. First, due to the proof-of-concept design the study was conducted in healthy individuals. Although this allowed us to control for a range of potential confounders, effects in patients and on the symptomatic level need to be systematically examined (27). Second, although the findings suggest that interactions between the RAS and the DA system may have contributed to the observed effect no direct measures of DA functioning were assessed and future molecular imaging studies are need.

In conclusion the present findings demonstrate that targeting the RAS via LT modulates the VTA-striatal-frontal cicruits during social reward and punishment processing. LT shifted the motivational significance of social reward vs punishment feedback and concomitantly modulated the VS-prefrontal pathways. During the

outcome phase LT attenuated VTA-insula coupling during social punishment yet enhanced the social PE in the VTA and DS suggesting attenuated sensitivity to social punishment in the context of enhanced adaptation. Together with the excellent safety profile of LT the findings may suggest a therapeutic property to enhance social motivation and attenuate the impact of negative social feedback.

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