Behavioral/Cognitive

The Angiotensin Antagonist Losartan Modulates Social Reward Motivation and Punishment Sensitivity via Modulating Midbrain-Striato-Frontal Circuits

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Social deficits and dysregulations in dopaminergic midbrain-striato-frontal circuits represent transdiagnostic symptoms across psychiatric disorders. Animal models suggest that interactions between the dopamine (DA) and renin-angiotensin system (RAS) may modulate learning and reward-related processes. The present study therefore examined the behavioral and neural effects of the Angiotensin II type 1 receptor (AT1R) antagonist losartan on social reward and punishment processing in humans. A preregistered randomized double-blind placebo-controlled between-subject pharmacological design was combined with a social incentive delay (SID) functional MRI (fMRI) paradigm during which subjects could avoid social punishment or gain social reward. Healthy volunteers received a single-dose of losartan (50 mg, n = 43, female = 17) or placebo (n = 44, female = 20). We evaluated reaction times (RTs) and emotional ratings as behavioral and activation and functional connectivity as neural outcomes. Relative to placebo, losartan modulated the reaction time and arousal differences between social punishment and social reward. On the neural level the losartan-enhanced motivational salience of social rewards was accompanied by stronger ventral striatum-prefrontal connectivity during reward anticipation. Losartan increased the reward-neutral difference in the ventral tegmental area (VTA) and attenuated VTA associated connectivity with the bilateral insula in response to punishment during the outcome phase. Thus, losartan modulated approach-avoidance motivation and emotional salience during social punishment versus 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.

Key words: dopamine; losartan; social reward; striatum; ventral tegmental area

Significance Statement

Social deficits and anhedonia characterize several mental disorders and have been linked to the midbrain-striato-frontal circuits of the brain. Based on initial findings from animal models we here combine the pharmacological blockade of the Angiotensin II type 1 receptor (AT1R) via losartan with functional MRI (fMRI) to demonstrate that AT1R blockade enhances the motivational salience of social rewards and attenuates the negative impact of social punishment via modulating the communication in the midbrain-striato-frontal circuits in humans. The findings demonstrate for the first time an important role of the AT1R in social reward processing in humans and render the AT1R as promising novel treatment target for social and motivational deficits in mental disorders.

Introduction

Adaptive processing of social feedback is vital for interperson-
Dysregulations in midbrain-striato-prefrontal circuits have been increasingly established as a core pathogenic mechanism across psychiatric disorders (Russo and Nestler, 2013; Fenzler et al., 2018). Human and animal studies suggest that this circuitry is involved in social reward and punishment processing (Dölen et al., 2013; Hung et al., 2017; Gu et al., 2019; Martins et al., 2021). Dopamine (DA) and its interactions with other neurotransmitter systems such as oxytocin play an important role in modulating social reward and punishment in these circuits (Nawijn et al., 2017; C. Grimm et al., 2021). However, direct pharmacological modulation of the DA systems commonly results in negative side effects (Pessiglione et al., 2006; O. Grimm et al., 2021) and effects of intranasal oxytocin are modulated by personal and contextual factors, including, e.g., sex, anxiety or social context (Bartz et al., 2011; Ma et al., 2018; Xin et al., 2020; Quintana et al., 2021). This poses a challenge for the clinical utility of these strategies.

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 (an approved treatment for hypertension) can modulate reward, threat processing and learning and memory in the absence of negative side effects (Marvar et al., 2014; Reinecke et al., 2018; Pulcu et al., 2019; F. Zhou et al., 2019; Swiercz et al., 2020; Xu et al., 2022; R. Zhang et al., 2022). 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 (Chai et al., 2000) and functionally significant Angiotensin II receptors located presynaptically on dopaminergic neurons (Mendelsonsohn et al., 1993; Brown et al., 1996). Losartan induced concentration-dependent inhibition of dopamine release via inactivation of AT1R (Narayanaswami et al., 2013), but also enhanced dopamine D1 receptor signaling which may contribute to both its effects on hypertension (D. Li et al., 2012) and reward-related processes (Maul et al., 2005; Hosseini et al., 2009). Together, the available evidence suggests that targeting the RAS via losartan may represent a promising candidate to modulate neurovascular processing in midbrain-striato-prefrontal circuits which mediate earlier stages of social and nonsocial reward processing to improve behavioral adaption (Izuma et al., 2008; Wake and Izuma, 2017; Gu et al., 2019; C. Grimm et al., 2021; Martins et al., 2021). Initial evidence for this strategy in humans comes from a recent study that demonstrated that a single dose of 50-mg losartan can modulate feedback-dependent learning in healthy individuals such that losartan enhanced the difference between loss and reward feedback learning rates and suppressed loss learning rates (Pulcu et al., 2019). While direct DA-mediated mechanisms of losartan cannot be interfered, it is conceivable that interactions between the RAS and the DA system may underly a modulation of the midbrain-striato-prefrontal circuits and associated functions such as reward-punishment balance.

We combined a preregistered randomized double-blind between-group placebo-controlled pharmacological experiment with a social incentive delay (SID) functional MRI (fMRI) paradigm (Nawijn et al., 2017) to examine whether social reward and punishment processing can be modulated by losartan, thus bridging the translational gap between animal models and human research as well as to determine losartan’s clinical potential. Behavioral indices reflecting motivation and subsequent emotional impact of social feedback, neural indices during reward and punishment anticipation and outcome served as primary outcomes. Based on previous findings we hypothesized that losartan would (1) enhance differential processing of reward and punishment on the behavioral level (Pulcu et al., 2019), which on the neural level would be reflected in (2) enhanced differential activation and connectivity in midbrain (i.e. ventral tegmental area, VTA), striatal and frontal circuits during social reward-punishment processing.

Materials and Methods
Design and participants
Ninety healthy participants (age range 18–27 years) were recruited for the randomized placebo-controlled between-subject pharmacological fMRI study which encompassed a single-dose administration of 50-mg losartan or placebo losartan or placebo tablets and subsequent administration of a social incentive delay fMRI paradigm (SID) with a demonstrated sensitivity to capture pharmacological modulations (Nawijn et al., 2017). A between-subject design was chosen to control for potential carry-over effects related to the repeated administration of the fMRI paradigm. All participants were free of a current or history of psychiatric or medical disorders as well as current and regular medication use. The present study thus represents a proof-of-concept trial examining whether losartan can modulate social reward and punishment processing on the behavioral and neural level. While this design in healthy subjects limits direct conclusions with respect to the effects in patients with psychiatric disorders or effects on psychiatric symptoms, the pharmacological imaging approach provides an elegant strategy to promote a neurofunctional characterization of novel pharmacological strategies (Nathan et al., 2014; Wandschneider and Koepp, 2016) and can facilitate translational progress (for losartan, see also Stout and Rischbrough, 2019).

Two participants were excluded because their baseline blood pressure was outside our predefined criteria, one participant was excluded because of technical failure during MRI acquisition. N = 87 subjects (N = 43, 26 males; losartan; N = 44, 24 males; placebo; Table 1) were included in the final analyses. Given the complexity of the modeling and fMRI analyses the sample size was based on recent between-subject pharmacological studies employing samples of 30–45 subjects to determine behavioral and neural effects of losartan (F. Zhou et al., 2019; Shkreli et al., 2020; Xu et al., 2022; R. Zhang et al., 2022).

Pharmacological and experimental procedure
Participants were stratified for sex and randomly allocated to treatment. Treatment was packed in identical capsules, counterbalanced across sexes and dispensed by an independent researcher. To reduce potential confounding effects of early life stress (Birn et al., 2017), impulsiveness, sensitivity to punishment and reward on reward-related neural processing the Childhood Trauma Questionnaire (CTQ; e.g., “Not enough to eat”), Barratt Impulsiveness Scale (BIS; e.g., “I plan tasks carefully”), and Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPRSQ, “Do you often refrain from doing something because you are afraid of it being illegal”) were administered at baseline (Fig. 1A; Barratt, 1959; Torrubia et al., 2001; Bernstein et al., 2003). Given that after oral administration losartan peak plasma levels are reached after 90 min with a terminal elimination half-life ranging from 1.5 to 2.5 h (Ohtawa et al., 1993; Lo et al., 1995; Sica et al., 2005) the experimental paradigm started 90 min after treatment (see also Michael et al., 2011; F. Zhou et al., 2019; Xu et al., 2022; R. Zhang et al., 2022). Losartan rapidly crosses the blood-brain barrier (Z. Li et al., 1993; Culman et al., 1999) and while effects at central receptors have been observed after 30 min after, i.e., administration effects on cardiovascular indices only become apparent after 3 h (Ohtawa et al., 1993; Pulcu et al., 2019; F. Zhou et al., 2019). To further control for potential confounding effects of losartan on cardiovascular activity blood pressure and heart rate were assessed before drug administration, as well as before and after the SID fMRI paradigm (Fig. 1A). To control for nonspecific affective effects of losartan the affective state of participants was tracked throughout.
Table 1. Participant demographics and control measures

| Characteristic         | Time       | LT, N = 43² | PLC, N = 44³ | Statistic⁴ | 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/m² |            | 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 (5.32)| 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        | 0.319   |
|                      | 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        | 0.297   |
|                       | 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)| 76.65 (11.31)| 1.6        | 0.121   |
|                       | Before MRI | 78.94 (11.23)| 69.73 (8.36)| 0.52       | 0.603   |
|                       | After MRI  | 69.70 (11.29)| 71.52 (11.94)| −0.75      | 0.456   |
| PANAS, negative affect | Baseline   | 16.58 (9.49)| 15.57 (8.16)| 0.31       | 0.756   |
|                       | Before MRI | 15.64 (8.73)| 14.53 (7.48)| 0.86       | 0.392   |
|                       | After MRI  | 14.86 (6.47)| 13.73 (3.82)| 1.0        | 0.323   |
| PANAS, positive affect | Baseline   | 21.27 (5.09)| 20.76 (5.92)| 1.3        | 0.213   |
|                       | Before MRI | 20.85 (6.38)| 19.41 (5.55)| 0.71       | 0.478   |
|                       | After MRI  | 21.68 (7.08)| 20.87 (10.00)| 1.0        | 0.297   |
| STAI, state anxiety    | Baseline   | 39.88 (7.27)| 39.41 (6.84)| −0.29       | 0.776   |
|                       | Before MRI | 39.50 (7.57)| 38.78 (7.87)| −0.16       | 0.870   |
|                       | After MRI  | 39.82 (6.87)| 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   |

² Descriptive statistics: mean (SD); n (%).
³ Statistical tests: Welch two-sample t test; Pearson’s χ² test.
⁴ Statistical tests: Welch two-sample t test; Pearson correlation; Welch’s F test; Pearson correlation.

The experiment via the Spielberger State-Trait Anxiety Inventory (STAI) and the Positive and Negative Affect Scale (PANAS) which were administered before drug administration, at the time of peak plasma concentrations and after the experiment (Spielberger et al., 1983; Watson et al., 1988). The subsequent affective impact of losartan-induced changes on social feedback processing was assessed via ratings of the cues before treatment, after fMRI, and following feedback stimuli after fMRI (Fig. 1A). In line with previous studies (Cremers et al., 2014; Nawijn et al., 2017), scrambled pictures were used as neutral outcomes to provide a close match in the perceptual features of the stimuli and control for potential differences in the salience of social and nonsocial stimuli.

Social incentive delay task
We employed a validated social incentive delay (SID) fMRI paradigm (Nawijn et al., 2017). 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, participants undergo a reaction time (RT) task which is followed by the presentation of a possibility-dependent social reward, punishment or neutral feedback (outcome; Fig. 1B,C). Participants received task instructions and a practice session before the formal experiment. During the practice session, all participants were informed about the types of outcomes that might be presented and that the corresponding outcome might or might not occur (no information on the probability was provided). During the formal 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; Fig. 1C). After a delay, the target was presented in the center of the 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 balanced and sufficient number of trials to support a robust analysis on the neural level the number of trials for each outcome was adopted by means of an adaptive algorithm. To this end, trial-wise reaction times (RTs) were recorded in real-time and employed to adjust the duration of the next target presentation to the individual performance. To this end, individual RTs were used to tailor the duration of target presentation to individual performance. The total duration consisted of the baseline time (500 ms) and a change time based on the adaptive algorithm that was initially evaluated in an independent sample with comparable demographic characteristics. If the response time of the participant exceeded the target time on a given trial for the reward condition the duration of the next target in the reward condition was increased by 60 ms, in case the participant responded in time the duration of the next trial was decreased by 40 ms for the punishment condition an increase of 20 ms or a decrease of 70 ms were employed. The individual adaptation in terms of increasing or decreasing the target duration times allowed to yield approximately 66.7% of reward-cue and punishment-cue trials being 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 intertrial interval and presentation of the condition-dependent 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., 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, dislikability, intensity, valence of cues and outcomes on a 9-point Likert scale after the fMRI session (Fig. 1A). In line with previous studies (Cremers et al., 2014; Nawijn et al., 2017), scrambled pictures were used as neutral outcomes to provide a close match in the perceptual features of the stimuli and control for potential differences in the salience of social and nonsocial stimuli.

Behavioral analysis
To maintain the trial-specific information of the SID task and increase sensitivity, a linear mixed model (R package ‘lme4’) was used with condition (social reward, punishment, neutral) and treatment (losartan, placebo) as two fixed factors and subject as random factor to account for individual adaptations of reaction time windows. Trials with no responses and RTs ≥ 3 SD on the individual level were removed.

Treatment effects on emotional perception ratings of cues and outcomes were examined with separate ANOVA and linear mixed models. The ANOVA on the affective ratings of the cues was conducted employing the R package ‘afex’ (https://CRAN.R-project.org/package=afex) with condition (reward, punishment, and neutral) and time (before and after experiment) as within-subject factors, and treatment (losartan and placebo) as between-subjects factor. To match the RT analysis and enhance the sensitivity a linear mixed model was used to analyze the ratings of outcome cues with condition (social reward, social punishment, etc.).
and neutral control) and treatment (losartan and placebo) as fixed factors and subject as a random factor.

MRI data acquisition and preprocessing
MRI data were acquired using a 3.0 Tesla GE MR750 system (General Electric Medical System). T1-weight high-resolution anatomic images were acquired with a spoiled gradient echo pulse sequence, repetition time (TR) = 6 ms, echo time (TE) = 2 ms, flip angle = 12°, field of view (FOV) = 256 × 256 mm, acquisition matrix = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm. Functional data were acquired using a T2*-weight echo planar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, acquisition matrix = 64 × 64, slice thickness = 3 mm, and 39 slices with an interleaved ascending order. Head movements were minimized by using comfortable head cushions. For each participant, 318 volumes were collected.

Preprocessing was fully implemented in fMRIPrep 20.2.1 (RRID:SCR_016216; Esteban et al., 2019), which is based on Nipype 1.5.1 (RRID:SCR_002823; Gorgolewski et al., 2011), 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; www.fil.ion.ucl.ac.uk/spm; Friston et al., 1994). For details about fMRIPrep steps, please see the following two sections.

Anatomical data preprocessing
A total of T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of CSF, white matter (WM), and gray matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823; Y. Zhang et al., 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray matter of Mindboggle (RRID:SCR_002438; Klein et al., 2017). Volume-based spatial normalization to the standard space (MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTS 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: FSL’s MNI ICBM 152 non-linear sixth Generation Asymmetric Average Brain Stereotaxic Registration Model (RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym; Evans et al., 2012).
For each of the two BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Susceptibility distortion correction (SDC) was omitted. The BOLD reference was then co-registered to the T1w reference using bregistr (FreeSurfer) which implements boundary-based registration (Greve and Fischl, 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcl flirt (FSL 5.0.9; Jenkinson et al., 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (RRID:SCR_005927; Cox and Hyde, 1997). The BOLD time-series (including slice-timing correction when reapplied onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD time-series were resampled into several standard spaces, correspondingly generating the following spatially-normalized, preprocessed BOLD runs: MN152NLin6Asym. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. The head-motion estimates calculated in the correction step were placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms time series from the subregion-specific seeds were treated as main physiological factors in the gPPI first level design matrix. In line with the BOLD level analysis session-specific regressors for the experimental conditions (reward, punishment) and identical control regressors were additionally included in the first level design matrix and motion parameters were included to improve motion control. 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.

Thresholding
ROI analyses were conducted in the R package ‘afex,’ and the statistical significance level set to p < 0.05. On the whole-brain level an initial cluster-forming threshold was set to voxel level p < 0.001, and statistical significance was determined via cluster-level inference and familywise error (FWE) control for multiple comparisons with p_{FWE} < 0.05 (Slotnick, 2017).

Data availability
Unthresholded group-level statistical maps are available via the OSF (https://osf.io/mnda4/). Other data of this study are available from the corresponding author upon reasonable request.

Results
Participants
Treatment 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 losartan.

Affective impact of the experimental manipulation
With respect to cue ratings, the ANOVA revealed significant main effects of arousal (time, F(1,84) = 17.04, p < 0.001; condition, F(1,94.162.63) = 13.58, p < 0.001), likeability (time, F(1,84) = 17.04, p < 0.001; condition, F(1,87.157.23) = 13.58, p < 0.001), dislikeability (condition, F(1,93.162.09) = 15.98, p < 0.001), intensity (time, F(1,84) = 35.85, p < 0.001; condition, F(1,97.165.82) = 10.42, p < 0.001), valence (condition, F(1,97.165.56) = 18.27, p < 0.001), and interaction effects of condition and time on likeability (F(1,94.163.02) = 6.37, p = 0.002) and dislikeability (F(1,95.163.92) = 3.22, p = 0.044). No significant treatment main or interaction effects were observed on capitalized on ultra-high field 7 T MRI to generate anatomically precise VTA maps (Trutti et al., 2021).

Exploratory functional connectivity analysis
No effect of condition was observed during anticipation in our a priori defined network encompassing the VS/DS/VTA (Fig. 2). To determine the social reward-punishment networks, we next 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 (Fig. 2C).

Based on our a priori regional hypotheses, combined with the a priori defined VS/DS/VTA masks and neural activity during receipt of feedback, 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 (McLaren et al., 2012). The extracted BOLD time series from the subregion-specific seeds were treated as main physiological factors in the gPPI first level design matrix. In line with the BOLD level analysis session-specific regressors for the experimental conditions (reward, punishment) and identical control regressors were additionally included in the first level design matrix and motion parameters were included to improve motion control. 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.

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cue ratings. The significant effect of time indicated that the experiment successfully induced stimulus-outcome associations.

Losartan effects on reaction time and affective response to outcome stimuli
The linear mixed model revealed a significant interaction effect ($F(2,5984) = 3.706$, $p = 0.025$; Fig. 1D; Table 2) between condition and treatment on reaction times indicating that losartan induced significantly stronger differences between social punishment versus social reward as compared with placebo ($t_{(1997)} = 2.679$, $p = 0.007$), reflecting a possibility of losartan mediated 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 significant condition main ($F(2,1997) = 404.983$, $p < 0.0001$; Fig. 1E) and condition times treatment interaction effects ($F(2,1997) = 4.914$, $p = 0.007$) on arousal ratings for outcomes. Post hoc analyses showed that losartan increased the reward-punishment difference ($t_{(1997)} = 2.390$, $p = 0.017$) and decreased punishment-neutral difference ($t_{(1997)} = -2.952$, $p = 0.003$) relative to placebo. With respect to dislikeability ratings for the outcomes, a linear mixed model revealed significant condition main ($F = 633.848$, $p < 0.0001$; Fig. 1F), and condition times treatment interaction effects ($F = 3.413$, $p = 0.033$). Post hoc tests showed that losartan increased the punishment-neutral difference ($t_{(1997)} = 2.597$, $p = 0.0095$) relative to placebo. No significant treatment main or interaction effects were observed on other outcome ratings (see Table 2).

Losartan effects on neural activation during anticipation and outcome phase
No significant main or interaction effects of treatment were observed in the a priori ROI analyses on extracted parameter estimates during anticipation. An exploratory whole-brain analysis confirmed the lack of significant treatment main and interaction effects (at $p_{FWE} < 0.05$). During the outcome phase a significant treatment times condition effect was observed in the VTA ($F(2,163) = 3.24$, $p = 0.0435$), reflecting that losartan significantly increased the difference between reward and neutral ($t_{(85)} = 2.407$, $p = 0.0172$) as well as between reward and punishment ($t_{(85)} = 1.924$, $p = 0.056$, marginal significant). For significant main effects of condition during the anticipation and outcome phase at whole-brain level, see Figure 2 and Table 3.

Losartan effects on VS-networks during anticipation
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...
Table 2. Losartan effects on reaction time and affective response to outcome stimuli

| Sum Sq | Mean Sq | NumDF | DenDF | F   | p   |
|--------|---------|-------|-------|-----|-----|
| Reaction time | | | | | |
| Treatment 5836.184 | 5836.184 | 1 | 85.0928 | 1.979 | 0.298 |
| Condition 27,729.964 | 13,864.982 | 2 | 5983.9603 | 2.607 | 0.074 |
| Interaction 39,417.958 | 19,709.797 | 2 | 5983.9603 | 3.706 | 0.025 |
| Arousal | | | | | |
| Treatment 1.166 | 1.166 | 1 | 85 | 0.466 | 0.497 |
| Condition 2028.444 | 1014.222 | 2 | 1997 | 404.983 | <0.0001 |
| Interaction 24.614 | 12.307 | 2 | 1997 | 4.914 | 0.007 |
| Likeability | | | | | |
| Treatment 0.014 | 0.014 | 1 | 85 | 0.005 | 0.943 |
| Condition 3697.834 | 1848.917 | 2 | 1997 | 689.416 | <0.0001 |
| Interaction 7.447 | 3.723 | 2 | 1997 | 3.413 | 0.033 |
| Dislikeability | | | | | |
| Treatment 0.285 | 0.285 | 1 | 85 | 0.087 | 0.769 |
| Condition 4166.394 | 2083.197 | 2 | 1997 | 633.846 | <0.0001 |
| Interaction 22.434 | 11.217 | 2 | 1997 | 4.914 | 0.007 |
| Intensity | | | | | |
| Treatment 3.201 | 3.201 | 1 | 85 | 1.197 | 0.277 |
| Condition 1913.460 | 956.730 | 2 | 1997 | 357.869 | <0.0001 |
| Interaction 14.011 | 7.006 | 2 | 1997 | 2.621 | 0.073 |
| Valence | | | | | |
| Treatment 0.647 | 0.647 | 1 | 85 | 0.300 | 0.586 |
| Condition 3506.816 | 1753.408 | 2 | 1997 | 812.378 | <0.0001 |
| Interaction 2.046 | 1.023 | 2 | 1997 | 0.474 | 0.623 |

Table 3. Brain activity during SID task

| Cluster region | Cluster size | x | y | z | F | p |
|----------------|--------------|---|---|---|---|---|
| Anticipation phase | | | | | | |
| Occipital lobe, parahippocam gyrus, fusiform, lingual gyrus | 2828 | 28 | -56 | -10 | 17.46 |
| Occipital lobe, MTG | 44 | -62 | -18 | 11.71 |
| Occipital lobe, temporal lobe | -26 | -70 | -6 | 11.64 |
| Outcome phase | | | | | | |
| Occipital lobe, tempal lobe | 13,431 | -20 | -98 | -8 | 107.19 |
| Occipital lobe, MTG | 26 | -96 | 0 | 96.68 |
| IFG, MFG, STG, insula, subcortical regions | 4928 | 20 | -2 | -14 | 39.05 |
| MFG, SFG, anterior cingulate | -18 | -4 | -14 | 31.17 |
| IFG, MFG, subcortical regions | 54 | 32 | 12 | 18.91 |
| Occipital lobe, MTG, STG, IFG, MFG, subcortical regions | 2132 | 4 | 62 | -8 | 15.07 |
| Occipital lobe, STG, MTG | -2 | 46 | 12 | 13.86 |
| Occipital lobe, STG, MTG, IFG, MFG, subcortical regions | 6 | 62 | 34 | 13.32 |
| (Reward + punishment) > neutral | | | | | | |
| Occipital lobe, tempal lobe | 30,964 | 26 | -96 | -4 | 18.53 |
| IFG, MFG, subcortical regions | -22 | -96 | -10 | 16.52 |
| IFG, MFG, anterior cingulate, supplementary motor area | 14 | 100 | 6 | 13.87 |
| SFG, MFG, anterior cingulate | 6288 | 2 | 52 | 34 | 8.69 |
| MFG | 8 | 60 | 36 | 8.10 |
| Cerebellum | 8 | 22 | 60 | 7.63 |

Discussion

The present pharmacological fMRI trial aimed to determine whether targeting the RAS system via losartan can modulate social reward and punishment processing via modulating VTA-striatal-frontal circuits. On the behavioral level losartan 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 losartan enhanced neural signals of the reward-neutral difference in the VTA while attenuating VTA-insula communication and concomitantly enhancing VTA-SFG communication during social punishment. Notably, several of our preregistered predictions with respect to a losartan-induced modulation of regional brain activity during the anticipation and outcome of social reward and punishment were not confirmed (except effects on the VTA). Instead, the results from the exploratory network level analyses provided a more complex picture of the regulatory effects of losartan on VTA-striato-frontal communication during reward-related processes. Together, these findings provide first insights into the regulatory role of the renin-angiotensin system on meso-striato-cortical pathways that may underly effects in the domain of punishment and reward processing.

On the behavioral level losartan modulated the motivational significance and arousal experience for social reward processing positively. This effect was mainly driven by prolonged reaction times during anticipation of and subsequently reduced arousal reaction toward social punishment stimuli. These findings partly align with observations in previous studies, such that following losartan healthy subjects perceived loss outcomes as being less informative resulting in an attenuated loss learning rate (Pulcu et al., 2019), and exhibited accelerated extinction, and decreased autonomous arousal, neural fear expression and an attenuated memory advantage for negative material (F. Zhou et al., 2019; Xu et al., 2022; R. Zhang et al.,...
Together, these observations indicate that losartan may attenuate the impact of negative information thus promoting a relative higher influence of anticipatory motivation and postencounter learning toward positive information.

On the neural level, the modulation of the approach-avoidance motivation between negative and positive social information was accompanied by a modulation of VS-frontal circuits, such that losartan 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 (Izuma et al., 2008; Gu et al., 2019; Martins et al., 2021). While the present study did not find a direct association between VS functional connectivity and behavioral changes, previous studies suggest that the pathways between the VS and frontal regions are critically involved in associated social processes including motivational and reinforcing aspects of social interactions (Murugan et al., 2017; Modi and Sahin, 2019). 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 (I. Gordon et al., 2016; Greene et al., 2018), and effects on this circuit may thus reflect a potential mechanism via which losartan can increase social motivation.

In contrast to the modulation of VS-centered circuits during the anticipation stage, losartan specifically modulated VTA

![Figure 3. Effects of losartan 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 cluster. 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.](image-url)
activity as well as its connectivity with insular and frontal regions during the outcome phase. During the social feedback presentation stage losartan 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 dopaminergic reward processing and learning circuits (Averbeck and Costa, 2017; Sharpe et al., 2017; C. Grimm et al., 2021) and together with the amygdala drives dopaminergic signaling in response to social stimuli (Modi and Sahin, 2019; C. Grimm et al., 2021), suggesting that losartan rendered positive social signals as more salient. In contrast, losartan 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 (Uddin, 2015; C. Zhou et al., 2020). This suggests that losartan 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.

From a functional neuroanatomy perspective losartan 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 (networks) were modulated during outcome. This dissociation aligns with the distinct functions of these core nodes in feedback-associated social and nonsocial processes (X. Zhou et al., 2019; E.M. Gordon et al., 2021; Suzuki et al., 2021). The VTA encompasses the majority of dopaminergic cell bodies and is strongly involved in predicting outcomes including social error signals and guiding flexible adaptation (Birn et al., 2017; Hétu et al., 2017; Gu et al., 2019; C. Grimm et al., 2021), whereas the VS which receives dopaminergic projections from the VTA, is strongly involved in appetitive motivation and reward-expectation for both social and nonsocial feedback (Gu et al., 2019; Martins et al., 2021) while the DS is stronger involved in learning, action initiation, and habit formation (Klugah-Brown et al., 2020; Suzuki et al., 2021). Although most of these functions encompass social as well as nonsocial processes, their critical role in reward and punishment processing critically influences social behavior (Mogull et al., 2017; Modi and Sahin, 2019; Zhang and Gläscher, 2020). The process-specific effects of losartan 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 disorders, including depression (Russo and Nestler, 2013; D. Zhang et al., 2020), social anxiety disorder (Cremers et al., 2014), post-traumatic stress disorder (Fenster et al., 2018), autism spectrum disorder (Delmonte et al., 2013), and schizophrenia (Mow et al., 2020). Together with accumulating evidence from previous studies (Reinecke et al., 2018; Pulcu et al., 2019; F. Zhou et al., 2019), our findings suggest that losartan 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.

Findings and interpretation need to be considered within the context of limitations. First, research in humans has only recently begun to explore the role of the renin-angiotensin system in cognitive, emotional and reward-related processes and the underlying neurobiological mechanisms (Reinecke et al., 2018; F. Zhou et al., 2019). An overarching framework of the regulatory role of the renin-angiotensin system in these domains is therefore currently lacking which limits the mechanistic interpretation of the present findings. Second, the proof-of-concept study was conducted in healthy individuals. Together with animal and population based studies pharmacological imaging studies in healthy subjects represent important steps to determine the translational potential of losartan (e.g., see also Marvar et al., 2014; F. Zhou et al., 2019; Seligowski et al., 2021). However, it is still possible that the novel strategy fails in patients (Stein et al., 2021) or effects are overshadowed by strong expectancy effects (Torregrossa, 2021). Effects in patients and on the symptomatic level thus need to be systematically examined. Third, given that our present study is the first to examine losartan effects on social reward we focused on a single dose. Although the findings may provide indirect support for a RAS and DA system interaction the lack of direct measures of DA functioning limit conclusions in this respect. Chronic and dose-dependent effects of losartan on midbrain-striatal-frontal circuits [see Kou et al. (2022) for acute vs chronic effects of a neuropeptide] as well as alternative mechanisms such as systemic effects of losartan on lipid and glucose metabolism (Schupp et al., 2006) remain to be addressed in future studies. Fourth, an additional analysis found that the guess accuracy for the correct treatment was significantly higher in the placebo group, which indicates that most of participants were considering to be under placebo. Although an additional analysis did not reveal interaction effects between treatment guess and treatment the high rates of placebo treatment expectation in both groups may have led to an attenuation of the treatment effects. Finally, we focused on social reward processing which may be more relevant for the clinical application and may have a higher ecological validity. Although some initial studies indicate that losartan may affect reward and punishment processing in monetary reinforcement learning paradigms (Pulcu et al., 2019; Xu et al., 2022), future studies are required to investigate whether the effects generalize to nonsocial feedback in incentive delay paradigms and to other types of natural rewards.

In conclusion, the present findings demonstrate that targeting the RAS via losartan modulates the VTA-striatal-frontal circuits during social feedback processing. Losartan modulated the motivational significance of social reward versus punishment feedback and concomitantly modulated the VS-prefrontal pathways. During the outcome phase losartan attenuated VTA-insula

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**Table 4. Functional connectivity results**

| Cluster region          | Cluster size | x     | y     | z     | F value |
|-------------------------|--------------|-------|-------|-------|---------|
| Anticipation phase, VS seed | 573          | 38    | 33    |       | 13.69   |
| MIG                     | 70           | 38    | 38    |       | 11.41   |
| L insula, STG           | 128          | 427   |       |       | 15.16   |
| R insula, putamen       | 128          | 246   |       |       | 14.09   |
| SFG                     | 128          | 213   |       |       | 11.75   |

All clusters passed the threshold at whole-brain cluster level $p_{clus} < 0.05$. L = left, R = right, SFG = superior frontal gyrus, MIG = middle frontal gyrus, STG = superior temporal gyrus.
coupling during social punishment suggesting attenuated sensitivity to social punishment. Together with the excellent safety profile of losartan the findings may suggest a therapeutic property to enhance social motivation and attenuate the impact of negative social feedback.

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