

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

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Abstract

Background 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. **Methods** 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. **Results** 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. **Conclusions** 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.

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 disorders including depression (1-3), social anxiety disorder (SAD) (4), post-traumatic stress disorder (PTSD) (5), addiction (6), autism spectrum disorder (ASD) (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 circuits (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 adaptation 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 circuits (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 activation 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 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 (5). N = 87 subjects (N=43, 26 males, LT; N=44, 24 males, PLC; **Table 1**) were included in the final analyses (exclusion see **supplementary method**).

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 (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 (see also(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. (26, 29, 50)). 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 SID fMRI paradigm (**Figure 1A** , details **supplementary methods**). To control for nonspecific affective effects of LT the affective state of participants was tracked throughout 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). 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, the study was approved by the local institutional ethics committee, all procedure followed the Declaration of Helsinki, and all procedures were preregistered (NCT04604756, URL:<https://clinicaltrials.gov/ct2/show/NCT04604756>).

Social incentive delay task

We employed a validated social incentive delay (SID) fMRI paradigm (5). 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 task which is followed by the presentation of a performance-dependent social reward, punishment or neutral feedback (outcome) (**Figure 1B-C**).

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 $\pm 3SD$ 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 3T GE MR750 system. Preprocessing was fully implemented in fMRIPrep (58) except for smoothing with a Gaussian kernel at full width at half maximum (FWHM, 8×8×8mm) conducted in SPM12 (Wellcome Department of Cognitive Neurology, London, UK,<http://www.fil.ion.ac.uk/spm/software/spm12>) (59). Details see **supplementary method** .

Individual- and group-level BOLD fMRI analyses

On the first-level the SID task was modeled in line with previous studies (2, 60-62), including condition- (social reward, social punishment, neutral) and phase- (anticipation, outcome) specific regressors (see **supplementary method**). 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 masks 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 the neutral condition, the prediction error for each trial was only computed for the social reward and social punishment conditions and employed as 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) according to

$$PE_t = R_t - EV_t$$

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

PE reflects the difference between the expectation and the actual outcome, and EV reflects the expectation of receiving a certain feedback on a given trial. 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 to 0.5 and -0.5 respectively. A learning rate $\alpha=0.7$ was used across participants (see 66, 69). 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. Although previous studies suggest that a range of learning rates (0.2-0.7) does not affect computation (66, 67, 69-71), additional tests with learning rate = 0.2 were conducted and confirmed the primary findings (see **supplementary results**).

For determining the social feedback PE on the neural level EV and PE were included on the first level as parametric modulators corresponding to anticipation and outcome phase respectively. On the first level the GLM models corresponded to the BOLD activation models and the EV and PE were included as parametric modulators. 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 initial 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

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 LT.

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**).

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 ($F = 3.24$, $p = 0.0435$), 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, see **supplementary results**). Significant main effects of condition during the anticipation and outcome phase see **supplementary results (Figure S1, 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 $p_{FWE} < 0.05$, **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 comparison 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.

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**).

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 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 activated 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 concomitant 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 ones involved 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). Although 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 disorders including depression (2, 3), SAD (4), PTSD (5, 15), ASD (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 with 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 circuits during social feedback 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/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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Legends to figures and tables

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 trials, social punishment feedback was shown in response to slow reactions on punishment trials.

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.

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.

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 tegment 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 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

Characteristic	Time	LT, N = 43	PLC, N = 44	Statistic	p value
Diastolic blood pressure	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
	Baseline	72.42 (6.59)	70.89 (6.93)	1.1	0.294
Heart rate	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
	Baseline	80.05 (12.50)	76.05 (11.31)	1.6	0.121
PANAS- negative affect	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
	Baseline	16.58 (4.99)	15.57 (4.41)	1.0	0.319
PANAS- positive affect	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
	Baseline	27.16 (5.97)	26.77 (5.51)	0.32	0.752
STAI- state anxiety	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
	Baseline	38.98 (7.27)	39.41 (6.84)	-0.29	0.776
STAI- trait anxiety	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
	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.

Table 2 Functional connectivity results

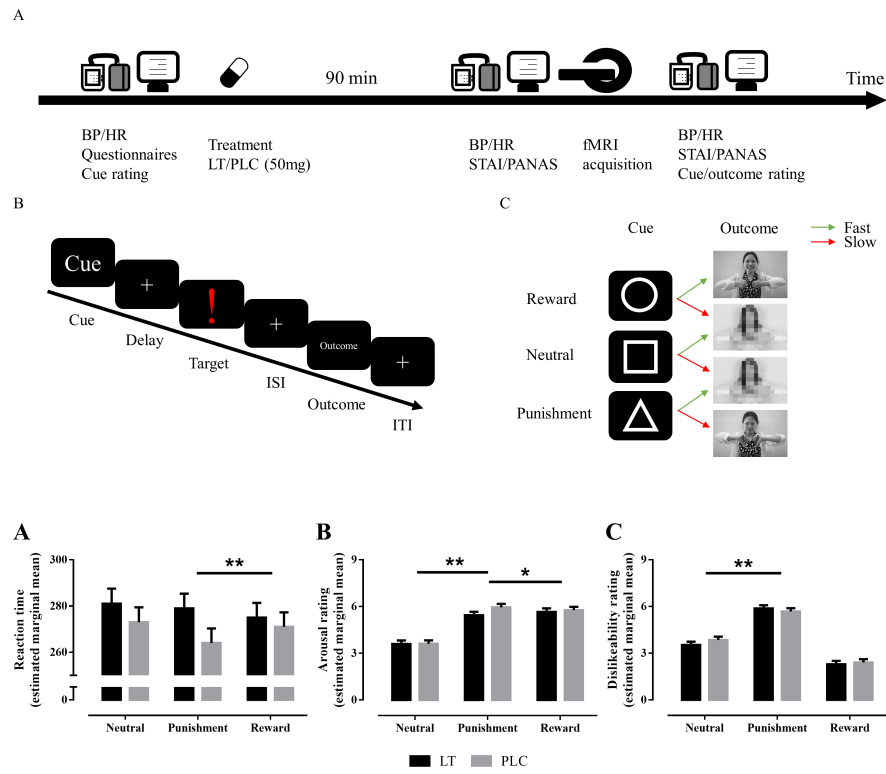
Cluster region	Cluster size	x	y	z	F value
Anticipation phase, VS seed	Anticipation phase, VS seed				
MFG	309	38	56	8	13.69
		38	60	16	11.41
Outcome phase, VTA seed	Outcome phase, VTA seed				
L insula, STG	427	-44	-22	-2	15.16
		-44	-6	0	12.50
		-40	6	-6	10.44
R insula, putamen	246	40	12	16	14.09
		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

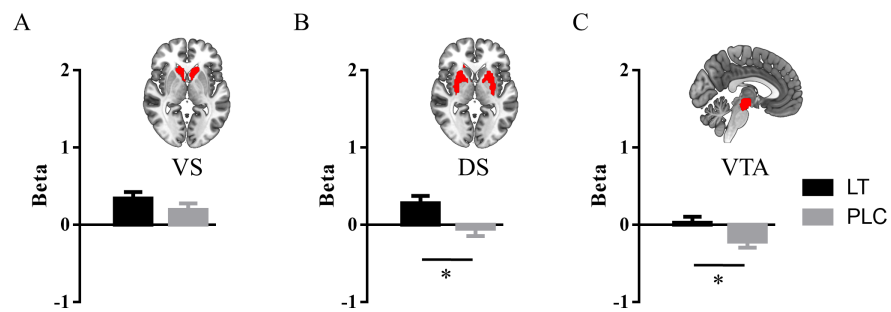
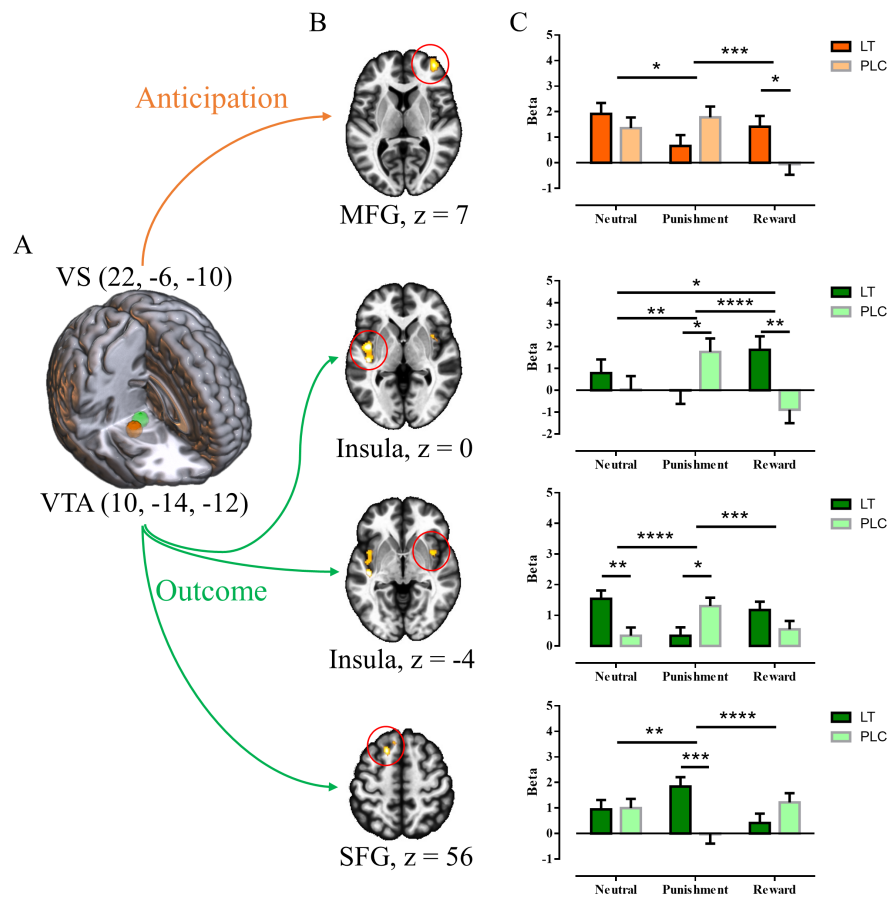
Note: All clusters passed the threshold at whole-brain cluster level $p_{FWE} < .05$. L = left, R = right, SFG = superior frontal gyrus, MFG = middle frontal gyrus, STG = superior temporal gyrus.

Table 3 Neural correlates of prediction error

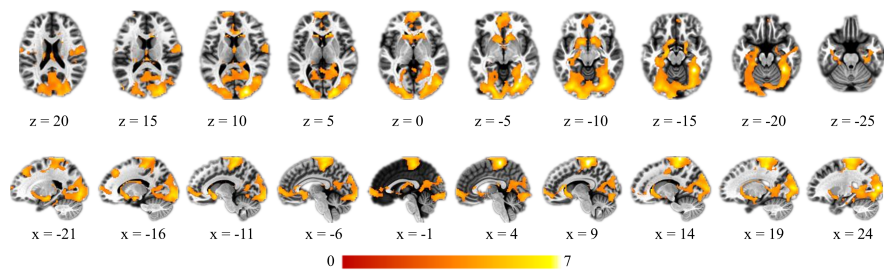
Cluster region	Cluster size	x	y	z	t value
Positive effects of PE	Positive effects of PE				
Parietal Lobe, mPFC, SFG, Precuneus	12731	8	-30	66	8.13
		14	-38	74	7.22
		20	-34	56	6.83
Occipital Lobe, Temporal Lobe, subcortical regions*	28095	36	-48	-16	7.92
		24	-92	8	7.21
		32	-80	-8	7.12
vmPFC, SFG, MFG, mPFC	733	-18	34	44	5.36
		-24	20	32	3.84
Negative effects of PE	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	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.

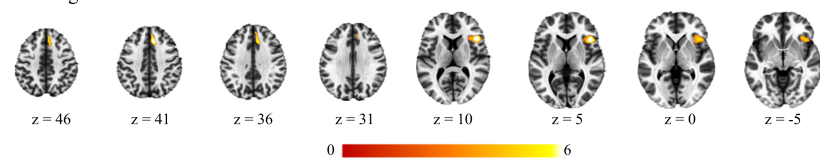




A. Positive effects of PE



B. Negative effects of PE



C. LT > PLC

