

The Effects of the Angiotensin II Receptor Antagonist Losartan on Appetitive Versus Aversive Learning: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND: Exposure therapy is a first-line treatment for anxiety disorders but remains ineffective in a large proportion of patients. A proposed mechanism of exposure involves inhibitory learning whereby the association between a stimulus and an aversive outcome is suppressed by a new association with an appetitive or neutral outcome. The blood pressure medication losartan augments fear extinction in rodents and may have similar synergistic effects on human exposure therapy, but the exact cognitive mechanisms underlying these effects remain unknown.

METHODS: We used a reinforcement learning paradigm with compound rewards and punishments to test the prediction that losartan augments learning from appetitive relative to aversive outcomes. In a double-blind parallel design, healthy volunteers were randomly assigned to single-dose losartan (50 mg) ($n = 28$) versus placebo ($n = 25$). Participants then performed a reinforcement learning task, which simultaneously probes appetitive and aversive learning. Participant choice behavior was analyzed using both a standard reinforcement learning model and analysis of choice switching behavior.

RESULTS: Losartan significantly reduced learning rates from aversive events (losses) when participants were first exposed to the novel task environment, while preserving learning from positive outcomes. The same effect was seen in choice switching behavior.

CONCLUSIONS: This study shows that losartan enhances learning from positive relative to negative events. This effect may represent a computationally defined neurocognitive mechanism by which the drug could enhance the effect of exposure in clinical populations.

Keywords: Anxiety, Appetitive learning, Aversive learning, Dopamine, Exposure therapy, Fear extinction, Losartan, Reinforcement learning

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Exposure—often thought of as an analog to fear extinction—is a key ingredient of effective cognitive behavioral therapy (1), the first-line intervention for anxiety disorders (2). However, treatment leads to recovery in only 50% to 60% of patients (3), with one half relapsing back into anxiety at some later point (4,5). A proposed mechanism of treatment action is a specific form of inhibitory learning whereby the previous association of a stimulus with threat is overwritten by a new association with safety (6–8). Within a reinforcement learning framework, this process can be described by the two learned associations being independently driven by prediction errors produced by the presence or absence of aversive and appetitive events, respectively. Strikingly, anxious individuals show deficits in this type of learning, reflected in elevated fear response to threat and safety stimuli during fear extinction (9–12). Such findings

may explain why response rates to treatment remain low, and they suggest that identifying strategies that compensate for such impairments may improve treatment response rates (7).

Recent preclinical and clinical work suggests that drugs targeting the renin-angiotensin system, such as the antihypertensive drug losartan, may represent a novel approach to the augmentation of exposure therapy. In a rodent model, these drugs have been shown to enhance fear extinction (13), and observational data from a large patient cohort indicates that use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers such as losartan while experiencing trauma is linked to developing fewer traumatic symptoms in the aftermath of that event (14). From a mechanistic perspective, these effects may be driven by central dopaminergic transmission, as angiotensin and dopamine receptors

have an overlapping neural topography, being collocated in brain areas involved in reward processing and fear learning (15–20). Furthermore, angiotensin receptors have been directly implicated in the modulation of reward-related dopamine release in the striatum (21), with the angiotensin II receptor antagonist losartan increasing excitatory dopamine D₁ receptor activation (22) and preventing dopaminergic cell deterioration in a Parkinson's disease cell line model (23).

These findings suggest a specific mechanism of action for losartan that spans its neural, cognitive, and behavioral effects: that is, it facilitates central dopaminergic transmission leading to enhanced learning from positive relative to negative events, which in turn produces a greater impact on exposure therapy. In this study, we took a computational approach to test the cognitive prediction arising from this proposal in human participants. We used an established reinforcement learning task in which stimuli were associated with independent positive and negative outcomes (24,25) with the volatility of the stimulus-outcome associations being varied independently. As volatile associations are more informative than stable ones (24), this task allowed us to measure the degree to which participants learned from the positive and negative outcomes when they were equally informative or when one was more informative than the other. In line with the research reported above, we hypothesized that losartan would modulate the priority of learning between aversive and appetitive outcomes by increasing reward relative to loss learning rates.

METHODS AND MATERIALS

Participants

The study was approved by the Oxford University research ethics committee. All participants gave written informed consent. Through local advertisements, 53 healthy participants were recruited. We estimated sample size based on the only available study on the effect of losartan on cognitive function in healthy volunteers (26). With observed prospective mean (SD) memory detection rates of 3.9 (2.4) after placebo and 5.7 (1.6) after losartan, calculations recommended 21 participants per group to detect an effect size $d = 0.9$ and statistical power of 80% (α level .05). We aimed for group sizes of 26 to account for potential dropout.

Main exclusion criterion was current DSM-IV Axis I disorder as assessed using the Structured Clinical Interview for DSM-IV (27). Participants also had to be medication free for at least 6 weeks, have a body mass index of 18 to 30 kg/m², and have no first-degree family member with a history of severe psychiatric disease. Participants were asked to refrain from excessive caffeine before the study.

Materials and Study Design

To characterize the sample, all participants completed the Anxiety Sensitivity Index Revised (28), neuroticism subscale of the Eysenck Personality Questionnaire (29), Behavioral Inhibition Scale (30), Beck Depression Inventory II (31), and Attentional Control Scale (32). The National Adult Reading Test (33) was applied to estimate verbal intelligence. Participants were stratified for gender and randomly allocated to one of two treatment conditions in a double-blind design: losartan

(Cozaar; Merck Sharp & Dohme Ltd., Hertfordshire, UK) given as a single oral 50-mg dose or matched placebo (microcrystalline cellulose [Rayotabs; Rayonex Biomedical GmbH, Lennestadt, Germany]). The randomization sequence was generated by a researcher not in direct contact with participants using a random number generator (www.random.org). Testing took place 1 hour after medication administration, when drug peak plasma levels are typically reached (34,35).

To assess potential changes in state mood and physiological symptoms, participants completed visual analog scales before administration of medication and before testing, at which time we also measured heart rate and blood pressure using an Omron 705IT (Omron Corp., Kyoto, Japan) sphygmomanometer. After testing, both participant and experimenter guessed whether losartan or placebo had been given.

Information Bias Learning Task

The information bias learning task (IBLT) (Figure 1) has been described previously (24) and was presented on a laptop computer running Psychtoolbox software version 3.0 on MATLAB (The MathWorks, Inc., Natick, MA). On each trial, two abstract shapes (Agathodaimon font letters) were presented; participants chose one shape, and then one win outcome (15p) and one loss outcome (–15p) were presented, each associated with one of the shapes. Participants were asked to choose the shape that they believed would give the better outcome. The outcomes were independent, meaning that a particular shape could be associated with one, both, or neither of the win and loss outcomes (Figure 1C). As the two outcomes were independent, participants had to separately learn which shape the win outcome and which shape the loss outcome was likely to be associated with and integrate this information to judge which option was the better one to select in the current trial.

The task consists of two distinct phases (Figure 1B): an initial block of 80 trials in which both the win and the loss outcome reversed frequently (i.e., were volatile), and two further blocks of 80 trials each in which one outcome reversed frequently and the other remained stable. The order of the final two blocks was randomized across participants. The rationale for varying the volatility of the outcomes in the last two blocks has been described previously (24). In brief, outcomes that are volatile are more informative than stable outcomes and should lead to participants employing a higher learning rate. Therefore, the first block measures the degree to which participants learn preferentially from positive relative to negative outcomes, whereas the final two blocks estimate how participants adjust their learning to match the volatility of the outcomes. The effect of losartan could manifest either as differential learning in block 1 if it acted to specifically bias learning of affective outcomes or as an interaction with volatility in the final two blocks if it acted to bias the adaptation of learning to the outcome information content.

The task was self-paced with explicit rest between blocks. The same two stimuli (shape A and shape B) were used within each block but changed between blocks. On average, within each block both outcomes were associated with shape A on 50% of trials (the probability for shape B is $1 - \text{shape A}$); therefore outcomes were also associated with shape B on 50% of trials). For the stable block, this was achieved with a

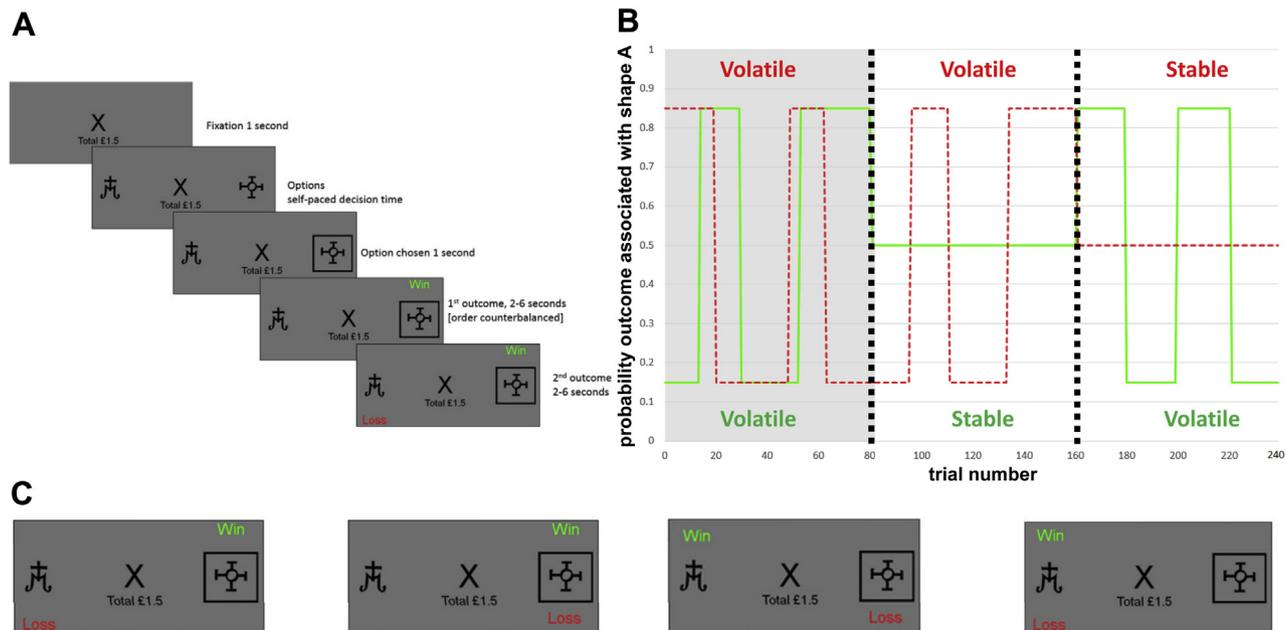


Figure 1. Experimental task design. **(A)** Timeline of one trial from the learning task. On each trial, participants were presented with two abstract shapes (e.g., shape A and B) and had to choose one. **(B)** Structure of the task. Each shape was associated with a win and loss probability, which were independent. We manipulated the volatility of these outcome probabilities in different task blocks (black vertical dashed lines separating each block containing 80 trials). In the first block (i.e., the first 80 trials of the task, gray shaded area), both outcomes were always equally volatile, which allowed an assessment of participants' learning bias. In the last two blocks (unshaded area), one outcome was volatile, whereas the other was stable. The y-axis represents the probability, p , that an outcome (win in solid green or loss in dashed red) will be found under shape A (the probability that it is under shape B is $1 - p$). **(C)** The independence of win and loss outcome probabilities means that a participant choosing shape A can experience four different outcomes. The independence of win and loss outcomes also meant that the participants had to separately estimate where the win and where the loss would be on each trial to perform optimally in this task. This manipulation made it possible to separately estimate learning from the win and loss outcomes. [Adapted with permission from Pulcu and Browning (24)].

constant association between the outcome and shape A of 50%, whereas in the volatile block the association shifted between 15% and 85% every 14 to 30 trials. Choice data were analyzed in two ways: fitting a reinforcement learning model and using a non-model-based approach.

Model-Based Analysis of Participant Choice Behavior

In line with our previous work (24), we analyzed choice behavior using a model in which a Rescorla-Wagner (36) learning component was coupled to a softmax action selector. This model separately estimates the probability of the two outcomes ($rwin$ and $rloss$) being associated with shape A on trial i .

$$rwin_{(i+1)} = rwin_{(i)} + \alpha win * (winout_{(i)} - rwin_{(i)})$$

$$rloss_{(i+1)} = rloss_{(i)} + \alpha loss * (lossout_{(i)} - rloss_{(i)})$$

Each process has its own learning rate (αwin and $\alpha loss$), which may take values between 0 and 1. $winout$ and $lossout$ represent the outcome of each trial, being 1 if the relevant outcome was associated with shape A and 0 otherwise. $rwin$ and $rloss$ were initialized at .5. These two estimated probabilities fed into an action selection stage:

$$pchoiceA_{(i)} = \frac{1}{1 + \exp^{-(\beta(rwin_{(i)} - rloss_{(i)} + \phi))}}$$

Here, $pchoiceA$ is the probability the model will select shape A on the current trial, β is an inverse temperature term that controls the degree to which the model's choices are driven by the learned probabilities, and ϕ is a bias term that allows the model to prefer one shape over the other. This model has four free parameters (two learning rates, one inverse temperature, and one bias parameter). Parameter values were estimated by calculating the joint posterior probability of parameters over the parameter space, given the choice of participants (24,25). The estimated value of each parameter was then calculated as the expected value of the parameter's marginal distribution. Separate parameters were estimated for each participant and each block. Details of model selection, comparing this with alternative models, are provided in the Supplement.

Non-Model-Based Analysis of Participant Choice Behavior

Non-model-based analyses can complement model-based analyses by illustrating the behavioral effect of the intervention in the absence of the assumptions associated with specific models (24). The IBLT includes trials in which both the win and the loss outcomes are associated with the same shape (Figure 1C). These trials are particularly useful because they motivate choice behavior for the following trial in opposing directions. Specifically, if a participant were more influenced by wins than losses, the participant would be more likely to stick with the choice he or she made if it was associated with both

Table 1. Sociodemographic and Clinical Characteristics of Participants in the Placebo and Losartan Groups

	Placebo (<i>n</i> = 25)	Losartan (<i>n</i> = 28)
Sociodemographic Data		
Gender, female/male, <i>n</i>	17/8	19/9
Age, years	25.4 (7.3)	26.3 (7.0)
Verbal IQ, NART	117.2 (2.8)	117.4 (13.8)
Clinical and Personality Measures		
Trait anxiety, STAI	35.0 (8.0)	34.4 (7.8)
Anxiety Sensitivity Index	14.5 (11.1)	16.0 (14.2)
Behavioral Activation Scale	24.3 (4.8)	24.8 (5.0)
Behavioral Inhibition Scale	14.8 (3.7)	15.0 (4.4)
Beck Depression Inventory	2.6 (3.4)	2.8 (4.3)
Neuroticism, EPQ	7.4 (4.9)	6.4 (5.1)
Attentional Control Scale		
Total	57.0 (7.2)	57.6 (8.1)
Focusing	24.8 (3.7)	25.5 (3.7)
Shifting	32.1 (5.6)	32.1 (5.3)

All values are presented as mean (SD) except where noted.

EPQ, Eysenck Personality Questionnaire; NART, National Adult Reading Test; STAI, State-Trait Anxiety Inventory.

outcomes and to switch if the choice was associated with neither outcome. In contrast, if a participant were more influenced by losses, the participant would show the opposite pattern, switching more often after choosing the shape associated with both outcomes. The simplicity of this analysis comes at the cost of precision—in contrast to model-based approaches, it is unable to differentiate an increase in the influence of wins from a decrease in the influence of losses and reports only the relative influence of wins versus losses. Note that trials in which the win and loss outcomes are associated with different shapes are less informative here, as in this case both outcomes encourage the same behavior (repeated selection of the shape associated with the win).

Statistical Analysis

We used two-tailed tests and $\alpha = .05$ in IBM SPSS Version 25 software (IBM Corp., Armonk, NY). Potential drug-induced changes in physiological and visual analog scale parameters were assessed using 2 time (baseline, peak) \times 2 group (placebo, losartan) mixed model analyses of variance. Choice behavior from the first block of the IBLT was analyzed separately from the last two blocks, as these assess different effects. The effect of losartan on the parameters derived from the model-based analyses were assessed using mixed-model analyses of variance with the within-subject factors valence (positive, negative) and block (only for analysis of last 2 blocks; win volatile, loss volatile) and the between-subject factors group (losartan, placebo) and block order (only for analysis of last 2 blocks; win volatile first or second). A generalized estimating equation framework using a logistic-link function was used to analyze non-model-based results, as the dependent variable in these analyses is the proportion of trials in which choice switching occurred. Within-subject factors were trial type (both outcomes associated with chosen shape, neither outcomes associated with chosen shape) and block type (for analysis of last 2 blocks only) with between-subject factors

group and block order. Decision reaction times (which were analyzed to assess for gross effects of losartan on processing speed) were Box-Cox transformed (37). Learning rates were transformed to the infinite real line before analyses, using inverse logistic transform (results are reported in normal space for ease of interpretation).

RESULTS

Demographics and Drug Side Effects

The groups (placebo, *n* = 25; losartan, *n* = 28) were well balanced on sociodemographic and clinical parameters. There were no differences in heart rate, blood pressure, and visual analog scale changes from baseline to drug peak level (Tables 1 and 2). Neither experimenter nor participants were able to correctly guess group allocation (losartan guesses; experimenter placebo 36%, losartan 48%, $p = .41$; participant placebo 36%, losartan 30%, $p = .77$), suggesting that double-blind study format was maintained.

Information Bias Learning Task

Model-Based Analysis. Losartan, relative to placebo, produced a significant positive relative to negative bias in learning rates in the first block (valence \times group interaction: $F_{1,49} = 5.110$, $p = .028$). Losartan suppressed loss learning rates relative to placebo ($t_{51} = -2.029$, $p = .048$, Cohen's $d = 0.54$), while leaving win learning rates intact ($t_{51} = 0.562$, $p = .58$). Win learning rates were significantly higher than loss learning rates in the losartan group ($t_{27} = 3.301$, $p = .003$, Cohen's $d = 0.69$), whereas these were comparable after placebo ($t_{24} = 0.032$, $p = .974$) (Figure 2A). The addition of gender and trait anxiety scores to the analysis of loss learning rates did

Table 2. Heart Rate, Blood Pressure, and Visual Analog Scale Ratings in the Two Groups Before Drug Intake and at Drug Peak Level

	Baseline		Drug Peak		<i>F</i> Test, <i>p</i> Value
	Placebo	Losartan	Placebo	Losartan	
Physiological Measures					
Heart rate	76 (12)	75 (14)	70 (11)	65 (9)	.19
Systolic blood pressure	119 (13)	120 (16)	115 (11)	117 (12)	.55
Diastolic blood pressure	70 (8)	75 (10)	70 (7)	73 (10)	.52
Visual Analog Scale Ratings					
Anxious	13 (18)	20 (26)	10 (16)	10 (13)	.21
Tearful	6 (12)	5 (9)	5 (9)	3 (6)	.86
Hopeless	8 (16)	6 (10)	5 (11)	3 (6)	.75
Sad	8 (13)	8 (14)	7 (13)	5 (8)	.36
Depressed	6 (12)	8 (15)	6 (15)	6 (11)	.37
Sleepy	28 (24)	21 (23)	20 (18)	19 (19)	.21
Nauseous	5 (9)	7 (16)	3 (5)	6 (10)	.77
Dizzy	9 (18)	5 (14)	7 (11)	5 (11)	.36
Heart racing	6 (12)	7 (15)	4 (7)	3 (8)	.93
Alert	47 (31)	42 (28)	48 (33)	37 (28)	.18

Values are presented as mean (SD). *F* tests show the interaction of group (placebo, losartan) \times time (baseline, drug peak).

Losartan and Reinforcement Learning

not influence the results (main effect of losartan: $F_{1,51} = 4.115$, $p = .048$).

Losartan did not influence learning rate adjustment in response to outcome volatility in the final two blocks (group \times block \times valence interaction: $F_{1,49} = 0.101$, $p = .752$). Rather, all participants adjusted learning rates in response to outcome volatility as reported previously (29) (block \times valence interaction: $F_{1,49} = 41.942$, $p < .001$) (Figure 2B, C).

The effect of losartan was specific to the learning rate parameter from the model, with no effect observed for either the inverse temperature or bias terms (all $F_{1,49} < 0.902$, all $p > .407$) (Supplemental Figure S1). For completeness, the values of the four free parameters estimated under the best fitting model are visualized on a value map for the first block of the task, in which we showed the behavioral effect of losartan (Supplemental Figure S2).

Non-Model-Based Analysis. Losartan increased the influence of win relative to loss outcomes on learning behavior in the first block (group \times trial type interaction: Wald's $\chi^2_1 = 4.87$, $p = .027$) (Figure 3). Losartan participants switched choice significantly less often when selecting a shape associated with both win and loss (main effect group: Wald's $\chi^2_1 = 4.55$, $p = .033$). However, the groups were comparable in terms of choice switching probability after trials in which both outcomes were associated with the nonchosen shape (main effect of group: Wald's $\chi^2_1 = 0.003$, $p = .95$). Consistent with the model-based results, losartan had no effect on choice switching in the final two blocks (terms including group: Wald's $\chi^2_1 < 3.2$, $p > .07$). Losartan did not influence total amount of money won ($t_{51} = -0.34$, $p = .73$) or reaction times ($F_{1,49} = 0.06$, $p = .808$) (Supplemental Figure S3). Lastly, the expected correlation between model-based and non-model-based measures was found across participants: the difference between win and loss learning rate was positively correlated with choice switch rate from trials in which neither outcome was associated with the chosen shape ($r_{52} = .67$, $p < .001$) and negatively correlated

with choice switch rate from trials in which both outcomes were associated with the chosen shape ($r_{52} = -.27$, $p = .049$).

DISCUSSION

We demonstrate that a single dose of the angiotensin II receptor antagonist losartan induces a positive learning bias in healthy human participants. More specifically, losartan reduced the degree to which participants were influenced by aversive outcomes, while leaving the influence of appetitive outcomes unaffected. These results suggest a potential cognitive mechanism by which losartan may influence the course of exposure therapy.

The task used in this study assessed the degree to which participant choice was influenced by both positive (wins) and negative (losses) outcomes. This was possible because the outcomes were independent—in other words, knowing where the win outcome would occur provided no information about where the loss outcome would occur and vice versa. As a result, participants had to separately learn the likely location of the two outcomes, allowing the influence of these estimates on choice behavior to be assessed. Losartan exerted a clear effect on choice switching behavior in the first block of the task; the choices of participants who had received losartan were more influenced by win than by loss outcomes. Specifically, participants who received losartan were significantly more likely to select the same shape in the trial after that shape had been associated with both outcomes and were less likely, albeit nonsignificantly, to switch their choice after choosing a shape associated with neither outcome. In other words, when the win and loss outcome drove choice behavior in opposite directions, participants who had received losartan were more likely to make a choice prompted by the win outcome. Whereas this analysis illustrates the basic effect of losartan, it estimates only the relative influence of the two outcomes and is therefore unable to determine whether participants were more influenced by the wins or less influenced by the losses. This level of analysis is possible using a computational

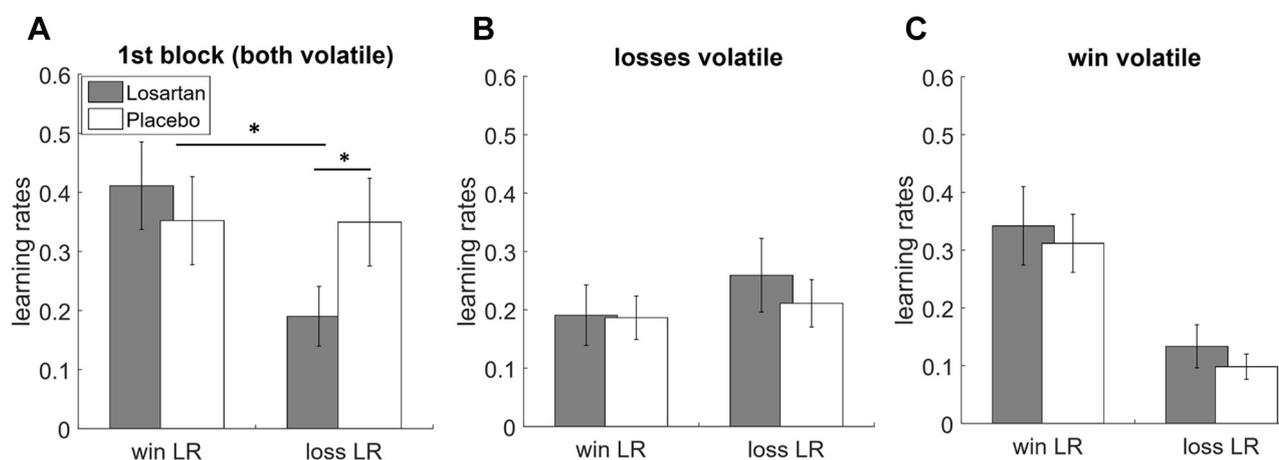


Figure 2. Behavioral effects of losartan on learning rates (LR) in different blocks of the information bias learning task. (A) Losartan altered LR for losses relative to wins ($F_{1,49} = 5.110$, $p = .028$). More specifically, the losartan group had significantly lower loss LR than the placebo group ($*p = .048$). (B, C) Losartan did not alter LR in the latter two blocks, in which one outcome was volatile and the other was stable. LR for wins and losses are represented separately. Mean \pm SEM are displayed.

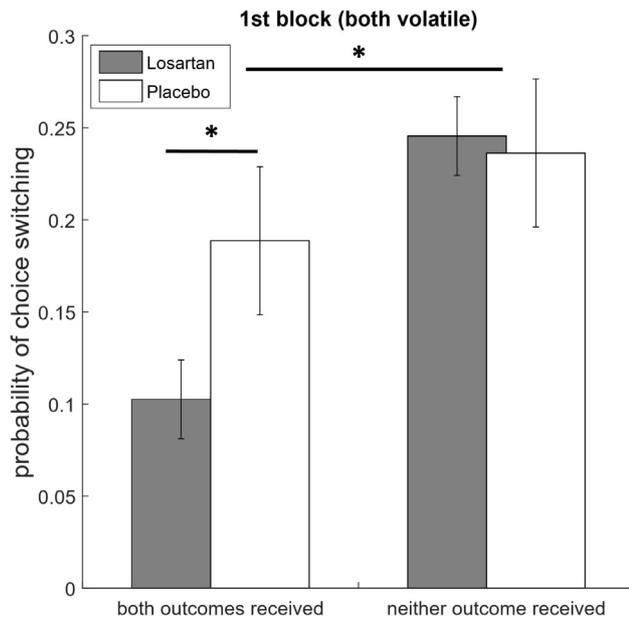


Figure 3. Choice switching analysis of learning behavior in the information bias learning task. Losartan increased the influence of win relative to loss outcomes on learning behavior in the first block of the information bias learning task (group \times trial type interaction: Wald's $\chi^2_1 = 4.87, p = .027$). Losartan significantly reduced participants' probability of switching to the unchosen shape after receiving both win and loss outcomes in the first block of the task (main effect of group: Wald's $\chi^2_1 = 4.55, p = .033$). *alpha-level of significance of $p < .05$.

modeling-based approach in which learning rates for the two outcomes can be independently estimated. Taking this approach revealed that losartan exerted a specific effect, suppressing the degree to which participants learned from negative outcomes, while leaving learning from positive outcomes intact. In effect, participants who received losartan treated the loss outcome as being less informative than participants who received placebo (24).

In contrast to its effect in the initial block of the IBLT, losartan did not influence the degree to which participants adjusted their learning rates in response to outcome volatility in the last two blocks. The volatility of an outcome influences how informative that outcome is (24). Normatively, learning rates should increase as the volatility of the association being estimated increases, as this is the most efficient learning strategy in dynamic environments (38). That losartan did not alter this process indicates that participants were still able to identify which of the two outcomes was most informative during learning, tuning their learning rates to this estimate, and that this effect dominated the valence-specific learning bias seen in the first block. In other words, losartan caused participants to initially bias their learning away from aversive outcomes, but they remained able to learn from those aversive outcomes if they estimated them to be informative. Consistent with this, losartan did not impair the overall performance of participants in terms of total monetary wins, the inverse temperature parameter, or reaction time. Previous work has found that anxiety is associated with an insensitivity to the volatility of negative outcomes (25). Our findings suggest that this

volatility-specific cognitive facet of anxiety is unlikely to be influenced by losartan, but rather the medication may act to reduce the general tendency to be more influenced by negative than positive outcomes.

A proposed key mechanism of action of exposure therapy is inhibitory learning, where the association of a stimulus with threat is suppressed by a new neutral or even positive association (6–8). A patient with panic disorder and agoraphobia may fear the onset of a heart attack if disconnected from the possibility of immediate medical help and therefore avoid situations such as large crowds or lonesome parks. Exposure tests out the anticipated aversive outcome of a heart attack and involves remaining in trigger situations for a prolonged period of time. The clinical effects of exposure are rooted in the patient making positive rather than the anticipated negative associations, leading to the anxiety decreasing gradually over time (39). In the present study, we found that losartan reduced learning from aversive events, while simultaneously preserving learning from positive outcomes. These effects are promising, as they suggest that losartan may have the potential to also facilitate positive relative to negative learning during exposure therapy in humans. Interestingly, we have recently reported that losartan increases the degree to which the amygdala differentially responds to appetitive and aversive stimuli in anxious participants (40). Better discrimination of appetitive and aversive stimuli, as demonstrated in this previous neuroimaging study, may represent an important mechanism by which losartan can induce the affective learning bias described in the current article.

Whereas the precise mechanism of action of losartan on learning and decision making is unclear, preclinical work provides some evidence that angiotensin II receptor activity may impact dopaminergic function. Losartan binding to the angiotensin II receptor is associated with increased activity of the dopamine D_1 receptor [albeit in kidney cells (22)], whereas administration of losartan reduces the release of dopamine in response to nicotine in striatal preparations (21) and inhibits cell death in a dopaminergic cell line (23). Although this work provides no conclusive evidence for the role of angiotensin II receptors, it suggests that the effect of losartan on fear extinction in rodents (13) and affective learning, as demonstrated by the current results, may be mediated via an effect on dopaminergic transmission. More generally, this work is consistent with an impact of losartan on reward-related processing, which has been linked to the development and treatment of anxiety disorders in humans. Research suggests that in anxiety disorders, neural response to reward is impaired (41,42), and impaired reward response has been linked to future onset of anxiety and impaired response to exposure therapy (43,44). In summary, while the detailed mechanism of action of losartan in exposure remains to be determined, the results from the current study are consistent with the idea that exposure-based treatments could be developed into more effective formats by combining them logically with pharmacological add-on compounds that synergistically target the balance between appetitive and aversive processing.

Similarly, our findings point to the possibility that losartan may prevent the development of anxiety symptoms that are triggered by unexpected traumatic events. A previous observational study revealed that being treated for high blood pressure using angiotensin-converting enzyme inhibitors or

angiotensin receptor blockers such as losartan while experiencing a trauma is associated with a reduced tendency to develop traumatic symptoms, with no such effects seen with other blood pressure medication (14). Whereas the a priori hypothesis of the current study was based on the relative learning from positive relative to negative outcomes, our finding of a specific suppression of learning from aversive events may provide a cognitive mechanism for this observation. From a practical perspective, it would be interesting to test whether the effect of losartan on these posttraumatic symptoms is evident if the drug is initiated shortly after trauma, as this may suggest a use for the medication in the prevention of posttraumatic stress disorder.

While these results are promising for the development of more effective combination treatments for anxiety disorders, there are limitations to their interpretation. First, the findings reported here are based on healthy volunteers only, and follow-up work in high-trait and clinically anxious populations will have to confirm their generalizability to these target populations. Also, even though our results provide evidence that losartan attenuates learning from aversive events, a mechanism proposed to underlie successful exposure therapy (6–8), no assessment of the efficacy of losartan in exposure has been completed, and the moderating effect of the decrease in aversive learning following losartan on clinically meaningful outcomes of exposure therapy remains to be tested. Finally, while we have speculated on a potential central dopaminergic mechanism underlying the observed effects of losartan, a number of alternative mechanisms may also be involved. Losartan crosses the blood-brain barrier (45) but also exerts a range of systemic effects, such as altering lipid and glucose metabolism via a non-angiotensin II receptor type 1 mechanism (46,47). Furthermore, administration of losartan produces a complementary increase in angiotensin II levels, which may exaggerate such off-target effects (48). Future work will need to address the exact biochemical mechanisms underlying the behavioral effects observed here.

Taken together, this study has identified a specific effect of losartan on a computationally defined learning parameter and suggests a role for angiotensin receptors in learning about aversive outcomes. We provide evidence that a single dose of the drug, in the absence of overall effects on blood pressure, heart rate, or transient mood changes, initiates a shift from aversive to appetitive learning. This mechanism has previously been suggested to be central to exposure therapy, hinting at the possibility that the effects observed here may positively interact with the clinical effects of exposure-based treatments.

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ClinicalTrials.gov: Losartan and Emotional Memory; <https://clinicaltrials.gov/ct2/show/NCT03763409>; NCT03763409.

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