Archival Report

Biological Psychiatry: GOS

Acute Angiotensin II Receptor Blockade Facilitates Parahippocampal Processing During Memory Encoding in High-Trait-Anxious Individuals

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ABSTRACT

BACKGROUND: Angiotensin II receptor blockers (ARBs) have been associated with preventing posttraumatic stress disorder symptom development and improving memory. However, the underlying neural mechanisms are poorly understood. This study investigated ARB effects on memory encoding and hippocampal functioning that have previously been implicated in posttraumatic stress disorder development.

METHODS: In a double-blind randomized design, 40 high-trait-anxious participants (33 women) received the ARB losartan (50 mg) or placebo. At drug peak level, participants encoded images of animals and landscapes before undergoing functional magnetic resonance imaging, where they viewed the encoded familiar images and unseen novel images to be memorized and classified as animals/landscapes. Memory recognition was assessed 1 hour after functional magnetic resonance imaging. To analyze neural effects, whole-brain analysis, hippocampus region-of-interest analysis, and exploratory multivariate pattern similarity analysis were employed.

RESULTS: ARBs facilitated parahippocampal processing. In the whole-brain analysis, losartan enhanced brain activity for familiar images in the parahippocampal gyrus (PHC), anterior cingulate cortex, and caudate. For novel images, losartan enhanced brain activity in the PHC only. Pattern similarity analysis showed that losartan increased neural stability in the PHC when processing novel and familiar images. However, there were no drug effects on memory recognition or hippocampal activation.

CONCLUSIONS: Given that the hippocampus receives major input from the PHC, our findings suggest that ARBs may modulate higher-order visual processing through parahippocampal involvement, potentially preserving intact memory input. Future research needs to directly investigate whether this effect may underlie the preventive effects of ARBs in the development of posttraumatic stress disorder.

https://doi.org/10.1016/j.bpsgos.2023.100286

In the past decade, research has increasingly implicated a key role of the renin-angiotensin system (RAS) in the development of anxiety and posttraumatic stress disorder (PTSD). Although this endocrine system is mainly involved in vascular contraction and blood pressure regulation (1), angiotensin II receptors are expressed in brain areas relevant for cognition and psychopathology, such as the amygdala and hippocampus (2). In rodents, increased angiotensin II levels are seen in response to stress, which plays a pivotal role in anxiety development (3,4). Importantly, drugs that target RAS activity—most notably angiotensin II receptor blockers (ARBs) such as losartan—have been associated with reduced PTSD symptom development in population-based studies (5,6), highlighting how studying the RAS in fear-related disorders may inform new curative and preventive developments.

Mechanistically, ARBs seem to target fundamental neurobiological processes in anxiety and PTSD. For example, single-dose losartan blunted the sympathetic stress response to highly distressing film material in a human PTSD model (7), while ARB administration in rodents directly reduced anxiety-like behavior (8,9). Similarly, ARBs improved fear extinction (6,10), the key learning mechanism underlying anxiety and PTSD treatment. Such previous work usually investigated the amygdala as the brain's "center of fear."

However, although anxiety and PTSD are both considered fear-related disorders, PTSD symptoms distinctively involve aberrations in episodic memory function, such as involuntary recall of traumatic events (memory intrusions). Thus, memory formation needs to be specifically addressed in human work, especially because the core brain area for episodic memory formation—the hippocampus—is modulated by ARB action (11): ARBs induced hippocampal neurogenesis in rodents (12,13), while reduced hippocampal neurogenesis has been associated with dysfunctional contextualization of memory

ISSN: 2667-1743

traces (14), which is believed to contribute to memory intrusions in PTSD (15).

Furthermore, preliminary evidence indicates that ARBs may counteract episodic memory aberrations often seen in PTSD (16,17) because ARBs have increased memory performance and prevented cognitive decline in elderly humans (18,19). Similar effects have been shown in rodents (13,20,21), where ARBs further enhanced hippocampal long-term potentiation (22), the core cellular mechanism in learning and memory (23). Notably, patients with PTSD perform more poorly than healthy control participants and trauma-exposed individuals on episodic memory tasks (16) that involve neutral (17,24,25) and emotional material (26), as well as autobiographical events (27). In turn, improvements in episodic memory performance were associated with PTSD symptom improvement post treatment in a longitudinal study (28), while symptom reduction was predicted by higher activity in the hippocampus and anterior cingulate cortex (ACC) during pretreatment memory encoding (28). Overall, such findings highlight hippocampus-dependent memory aberrations and their neural correlates as relevant markers in PTSD research and emphasize a potentially crucial role of the RAS in the memory system.

Given that 1) population-based studies have associated ARBs with PTSD symptom prevention (5,6), 2) PTSD is characterized by episodic memory aberrations (16,17), and 3) ARBs enhanced memory function (13,18–21), we investigated the effect of acute ARB administration on episodic memory encoding in high-trait-anxious volunteers to initiate PTSD applicability using a double-blind randomized design. Based on the rapid cognitive effects of losartan (7,29,30), we hypothesized that one dose would improve memory performance and enhance hippocampal processing during memory encoding. As the first experimental medicine study to date, we employed pattern similarity analysis (PSA) in addition to analyzing mean blood oxygen level–dependent (BOLD) signal changes. Instead of averaging the BOLD signal across voxels, PSA allows analysis of temporal changes in the stability of fine-grained spatial activity patterns within a brain area, which inherently represents more information than mean signals (31,32). Previous research has shown that the neural stability of activity patterns (i.e., higher pattern similarity) is not only associated with successful episodic memory formation but may also be a more sensitive neural marker of memory formation than mean BOLD signal (33–35). Due to the novelty of using such analysis in clinical research, we employed this approach in an exploratory post hoc way to allow for a more refined comprehension of the neural underpinnings of ARB mechanisms of action on the human memory system.

METHODS AND MATERIALS

Participants

We recruited 41 high-trait-anxiety participants (34 women) with a State-Trait Anxiety Inventory-Trait score >40 (36), based on sample size calculation (see the Supplement).

Participants were recruited from the public through posts on notice boards, social media, and mailing lists. They were included if they 1) were 18 to 50 years old, 2) had a body mass index of 18 to 30, 3) were not pregnant/breastfeeding, 4) smoked <5 cigarettes/day, 5) did not take any central nervous system active medication during the past 6 weeks, 6) were not taking any blood pressure medication or aliskiren, 7) did not suffer from serious medical conditions, 8) had no personal or family history of a severe psychiatric condition, and 9) had no contraindication to magnetic resonance imaging (MRI). Apart from demographics, the following questionnaires were included to describe the sample: the Eysenck Personality Questionnaire (37), Anxiety Sensitivity Index (38), Beck Depression Inventory-II (39), Attentional Control Scale (40), and Behavioral Inhibition and Activation Scale (41). All participants gave written informed consent.

Procedure

The study received ethics approval from the University of Oxford Medical Sciences Research Ethics Committee. During an online screening, participants were interviewed about their medical history followed by a psychiatric screening using the Structured Clinical Interview for DSM-5 (42), and the Spot-the-Word test (43) to estimate verbal intelligence. Eligible participants were invited to a face-to-face session and randomly allocated to receive either a single dose of 50 mg losartan (Merck Sharp & Dohme Ltd.) or placebo (microcrystalline cellulose; Rayotabs, Rayonex GmbH) and stratified by gender by an independent researcher to preserve double-blindedness. To account for potential confounding effects on cognitive outcomes, blood pressure and heart rate were measured before drug administration and at drug peak level (1 hour after intake) (44, 45) together with visual analog scales assessing physiological symptoms and mood state. Subsequently, participants completed the memory paradigm, which comprised a pre-scan encoding phase, pre-scan recognition test, main encoding phase during functional MRI (fMRI), and the main recognition test 1 hour after fMRI. Subsequently, participants and experimenter guessed group allocation.

Memory Paradigm

During pre-scan encoding, participants viewed the same 8 images (4 animals, 4 landscapes) 8 times in pseudorandom order (2 seconds per image, interstimulus interval 500 ms) to identify them as animals or landscapes. To ensure successful encoding, a short pre-scan recognition test followed containing the 8 encoded images and 8 new images to be recognized as old (i.e., seen during encoding) or new.

During the main fMRI encoding phase, participants were presented with 6 blocks containing the 8 images from the pre-scan encoding phase (familiar blocks) and 6 blocks of 8 images that had not previously been seen each time (novel blocks) in alternating order, with a 12-second fixation cross presentation between blocks as baseline. Within blocks, images were presented pseudorandomly for 2 seconds (interstimulus interval 500 ms) to be identified as animals or landscapes and memorized.

During the main recognition test, 1 hour after fMRI, participants were presented all images that were seen during fMRI (8 familiar, 48 novel) and 27 additional new images to be recognized as old (i.e., seen during fMRI) or new (see Figure 1 for an overview).

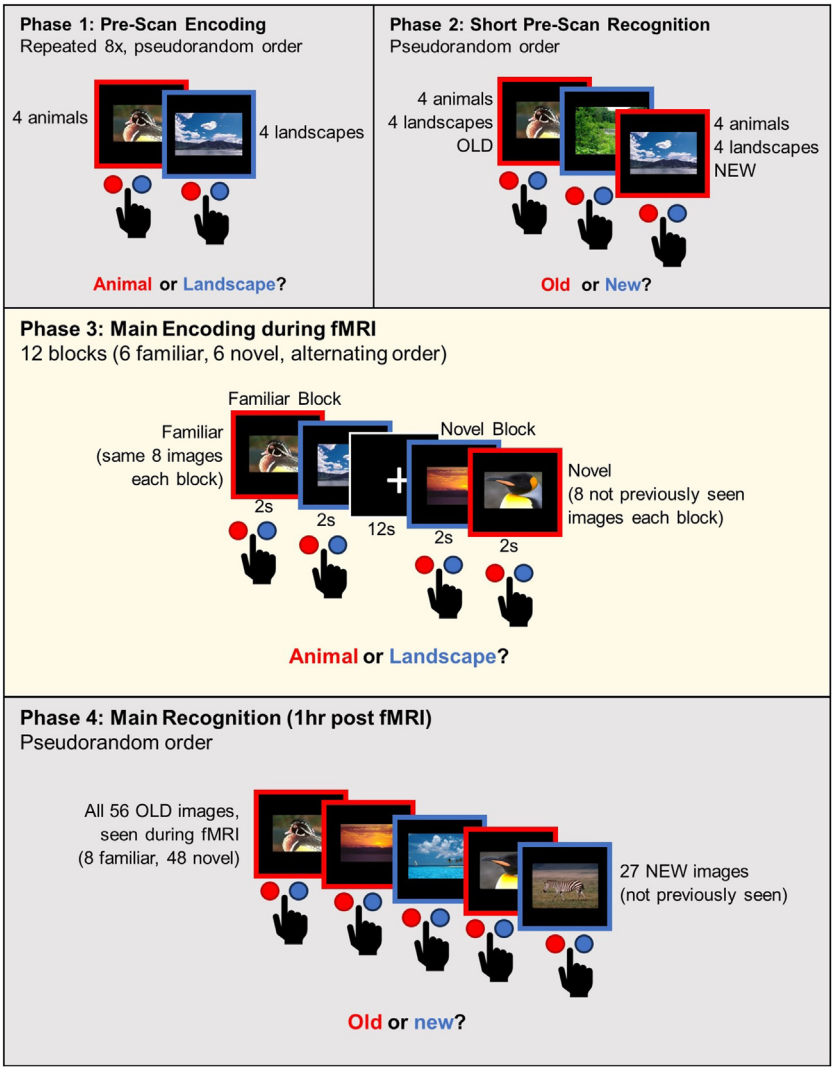

Figure 1. Overview of the memory task. During the pre-scan encoding phase (phase 1), participants were instructed to repeatedly identify the same 8 pictures as animals or landscapes. During the pre-scan recognition phase (phase 2), participants were presented with the 8 pictures from pre-scan encoding and 8 new pictures to be recognized as old or new. This serves to confirm the 8 images from pre-scan encoding (from here referred to as "familiar images") have been successfully remembered. In the main encoding phase during functional magnetic resonance imaging (fMRI) (phase 3), participants were presented with alternating blocks of the same 8 familiar images and blocks of images that had not previously been seen (from here referred to as "novel images"). They were instructed to identify the images as animals or landscapes and to memorize them. During the main recognition test (phase 4), participants indicated whether the images were old (i.e., 8 familiar images and 48 novel images that were seen during fMRI) or new (27 images not previously seen during any experimental phase). Note that only the main encoding phase (phase 3) was conducted during the fMRI scan.

MRI Data Acquisition and Analysis

MRI data was acquired at the Oxford Centre for Human Brain Activity using a 3T Siemens MAGNETOM Prisma scanner (Siemens) with a 32-channel head-coil. MRI preprocessing and analysis was conducted using FSL (http://www.fmrib.ox.ac.uk/fsl). For a description of MRI acquisition and preprocessing, see the Supplement.

Univariate Analysis. Statistical analyses were conducted with FEAT using a custom 3-column format convolved with a gamma hemodynamic response function for the general linear model (GLM). During first-level analyses, 1 regressor for familiar images and 1 for novel images were modeled including their temporal derivatives. The contrasts of interest were familiar > baseline, novel > baseline, familiar > novel, and novel > familiar. Individual activation maps were used for higher-level group contrasts (losartan vs. placebo) including gray matter maps to correct for potential volumetric differences. Whole-brain mixed-effects analysis with FLAME 1+2 and a cluster-based thresholding of $z > 3.1$ and a familywise error–corrected $p < .05$ was conducted. Additionally, we included a hippocampus region of interest (ROI) analysis based on a bilateral anatomical mask created using a 50% threshold on the Harvard-Oxford cortical structural atlas. We extracted BOLD signal parameter estimates from the hippocampus ROI to conduct a 2 × 2 mixed-model analysis of variance (ANOVA) with the between-factor drug group (losartan, placebo) and within-factor image condition (novel, familiar).

Pattern Similarity Analysis. To obtain a more fine-graded understanding of the cluster effects, we employed exploratory PSA. Due to the short interstimulus interval between picture presentations (500 ms), we could not employ PSA at the single-item level as has been recommended previously (46). Therefore, PSA was adapted from the single-item/trial design

to correspond to the block design in this study. For first-level analyses, we used FEAT by convolving 3-column format with a gamma hemodynamic response function for the GLM. Following previously published work (33–35,46,47), each block was modeled separately in a GLM in which one regressor represented the block of interest, and a second regressor was added with all other blocks of no interest, including both regressor's temporal derivatives. Each GLM had 1 contrast block of interest > baseline [for a review of PSA methodology, see (46)].

For group-level comparisons, we used custom MATLAB code. As ROIs, we used the anatomically defined hippocampus and each cluster identified in the univariate whole-brain analysis. Within each ROI, cross-voxel activity for each block was correlated using Fisher's *z*-transformed Spearman correlations (46). This leads to a pattern similarity (PS) score per block and participant. Then, we calculated the mean PS score for each condition (familiar × familiar, novel × novel) for each participant. To test for group differences in mean PS score between losartan and placebo, a group (losartan, placebo) × condition (novel, familiar) mixed-model ANOVA was conducted.

Behavioral Analysis

All analyses were performed using SPSS software version 29 (IBM SPSS, Inc.). To test for behavioral group differences in identification accuracy during encoding (i.e., the sum of images correctly identified as animals/landscapes) and memory recognition, we used independent samples 2-tailed *t* tests with an alpha level of 0.05. Memory recognition was reflected by the discrimination index P_r (P_r = hit rate − false alarm rate) (48), where hit rate refers to correctly classified old images and false alarm rate to incorrectly classified new images. Additionally, we employed a group (losartan, placebo) × condition (novel, familiar) mixed-model ANOVA on reaction times.

RESULTS

Participant Characteristics and Acute Drug Effects

The groups were comparable across all sociodemographic, clinical, attentional, and personality trait questionnaire measures (Table 1). There were no acute drug effects on blood pressure and heart rate (all *p*s > .08) (Table 2) or on changes in mood and physiological visual analog scale ratings from baseline to drug peak level, suggesting that losartan was well-tolerated and that any potential confounding effects of noticeable side effects on cognitive outcome markers were minimal. Drug administration was not correctly guessed above chance probability (participants 55% correct, experimenter 45% correct, both *p*s = .82), suggesting that double-blindedness was maintained.

One female participant was excluded from all analyses due to failure to encode familiar images despite repeated presentation (final sample $N = 40$).

Table 1. Overview of Sociodemographic Measures and Attentional, Clinical, and Personality Participant Characteristics

	Placebo, $n = 20$	Losartan, $n = 20$
Sociodemographic Measures		
Female, *n*	17	16
Age, years	27.15 (9.26)	27.17 (9.63)
Spot-the-Word test	100.14 (20.59)	107.53 (10.89)
Education, years	17.65 (3.48)	16.96 (2.44)
Attentional, Clinical, and Personality Measures		
ACS	46.20 (7.96)	48.69 (7.05)
BDI	11.40 (9.77)	9.50 (5.50)
BIS	12.20 (2.95)	12.60 (3.23)
BAS	26.60 (4.56)	24.65 (6.35)
ASI	14.0 (10.4)	16.5 (14.0)
STAI-T	48.65 (7.99)	43.73 (9.67)
EPQ – Psychosis	3.40 (2.76)	2.35 (2.72)
EPQ – Neuroticism	14.50 (4.43)	12.50 (5.22)
EPQ – Extraversion	10.72 (5.06)	13.95 (5.62)
EPQ – Lie	9.10 (3.57)	8.90 (3.14)

Values are presented as mean (SD) except where noted.

ACS, Attentional Control Scale; ASI, Anxiety Sensitivity Index; BAS, Behavioral Activation Scale; BDI, Beck Depression Inventory; BIS, Behavioral Inhibition Scale; EPQ, Eysenck Personality Questionnaire; STAI-T, State-Trait Anxiety Inventory-Trait.

Behavioral Task Analysis

Image Identification at Encoding. Both groups performed equally well at identifying images as animals or landscapes (% correct losartan: mean = 96.30%, SD = 11.49; placebo: mean = 95.31%, SD = 11.34; $t_{38} = -0.27$, $p = .79$, $d = -0.09$). The group (losartan, placebo) × condition (novel, familiar) ANOVA for response time revealed that both groups were faster at correctly identifying familiar images as animals/landscapes than correctly identifying novel images as animals/landscapes (familiar mean = 0.72 seconds, SD = 0.13; novel mean = 0.82 seconds, SD = 0.17; main effect condition $F_{1,38} = 79.32$, $p < .001$, $\eta_p^2 = 0.68$). This is expected because familiar images were presented repeatedly and therefore required less visual discrimination. While there was no main effect of group on response time ($F_{1,38} = 2.69$, $p = .11$, $\eta_p^2 = 0.07$), there was a trend for a group × condition interaction effect ($F_{1,38} = 3.55$, $p = .07$, $\eta_p^2 = 0.09$) wherein the losartan group was faster at identifying novel images as animals/landscapes (losartan mean = 0.77 seconds, SD = 0.15; placebo mean = 0.86 seconds, SD = 0.18, $t_{38} = 1.81$, $p = .08$, $d = 0.57$) but not familiar images (losartan mean = 0.70 seconds, SD = 0.12; placebo mean = 0.75 seconds, SD = 0.13, $t_{38} = 1.36$, $p = .18$, $d = 0.43$), potentially reflecting a drug-induced visual processing advantage for images that had not been seen previously (Figure S1).

Memory Recognition. An independent sample *t* test on the P_r score showed that there were no group differences in recognition performance (losartan: mean = 0.53, SD = 0.14; placebo: mean = 0.54, SD = 0.17; $t_{38} = 0.20$, $p = .85$, $d = 0.06$).

Memory Paradigm fMRI

Basic Task Effects. Task effects on neural memory encoding were determined by comparing the BOLD signal for novel versus familiar images across groups because novel images require memory formation in contrast to familiar images, which have already been encoded pre-fMRI. Consistent with

Table 2. Group Comparisons on Physiological Parameters and VAS Ratings Taken Before Drug Intake and at Drug Peak Level

	Baseline, Mean (SD)		Drug Peak Level, Mean (SD)		
	Placebo	Losartan	Placebo	Losartan	*p*
Physiological Measures					
Heart rate, beats/minute	78 (11)	78 (17)	69 (7)	70 (11)	.84
Systolic blood pressure, mm Hg	113 (12)	120 (15)	111 (11)	113 (14)	.31
Diastolic blood pressure, mm Hg	69 (8)	73 (11)	68 (8)	71 (11)	.96
VAS Rating					
Anxious	2.45 (2.35)	2.30 (2.03)	1.60 (1.79)	1.45 (1.73)	.99
Sleepy	2.30 (2.08)	2.90 (2.15)	2.15 (2.35)	2.70 (1.66)	.93
Flushed	1.85 (2.32)	1.45 (1.61)	0.60 (1.23)	0.25 (0.98)	.93
Tearful	0.45 (0.95)	0.65 (0.93)	0.15 (0.37)	0.25 (0.55)	.74
Nauseous	0.85 (1.76)	0.25 (0.55)	0.70 (1.46)	0.45 (0.76)	.09
Hopeless	0.75 (1.59)	0.55 (0.89)	0.60 (1.24)	0.25 (0.55)	.50
Tremor	0.30 (0.57)	0.40 (0.68)	0.25 (0.55)	0.30 (0.57)	.77
Sad	1.25 (1.65)	1.05 (1.00)	0.95 (1.57)	0.40 (0.68)	.29
Dizzy	0.20 (0.41)	0.25 (0.71)	0.60 (1.10)	0.55 (0.95)	.71
Depressed	1.25 (1.74)	0.70 (0.98)	0.80 (1.47)	0.50 (0.69)	.28
Heart racing	0.95 (1.28)	0.70 (1.03)	0.30 (0.73)	0.85 (1.05)	.08
Alert	5.05 (2.44)	5.65 (2.82)	4.40 (2.80)	4.35 (2.70)	.54

p Values refer to the statistical level of significance of the group × time interaction effect.
VAS, visual analog scale.

previous findings (49,50), the task activated the memory network consisting of visual occipital areas, temporal fusiform cortex, parahippocampal gyrus (PHC), and hippocampus (Figure 2A; for full cluster information, see Table S1).

Losartan Effects on Univariate BOLD Signal. Losartan administration changed the neural response to novel and familiar images. In the whole-brain analysis for familiar images (vs. baseline), 3 clusters were identified in which the BOLD signal was greater for the losartan group compared with placebo, including the PHC, ACC, and caudate (Figure 2B, C). For novel images (vs. baseline), 1 cluster in the PHC showed a greater BOLD signal in the losartan group compared with placebo (Figure 2B, C). Notably, both clusters in the PHC were located within the memory network identified by the basic task effects, although there were no significant group differences in the direct novel versus familiar contrasts (i.e., novel > familiar, novel < familiar).

In the hippocampus ROI, the group (losartan, placebo) × condition (familiar, novel) ANOVA showed greater BOLD signal in response to novel compared with familiar images across groups (novel: mean = 6.50, SD = 9.55; familiar: mean = 0.69, SD = 8.58; $F_{1,38} = 27.87$, $p < .001$, $\eta_p^2 = 0.42$). However, there was no main effect of group ($F_{1,38} = 0.35$, $p = .56$, $\eta_p^2 = 0.01$) and no group × condition interaction effect ($F_{1,38} = 0.38$, $p = .54$, $\eta_p^2 = 0.01$), suggesting that losartan did not modulate the hippocampal BOLD response. To explore whether losartan differentially affected BOLD response over the course of the task, such as having early effects that diminished over time, we conducted an exploratory group (losartan, placebo) × block (1–6) ANOVA for novel and familiar images. However, there were no group main effects or group × block interaction effects (all *p*s > .33) (Figure 3).

Losartan Effects on Multivariate PSA. We conducted PSA to explore whether losartan affected neural stability during memory encoding in the identified univariate clusters (ACC, caudate, and a single PHC ROI combining both PHC clusters) and the anatomically defined hippocampus. Because we employed PSA on a block level, PS reflected the neural stability of a cognitive process rather than the neural stability of an item representation when employed on a single trial/item level [for PS interpretation, see (46)].

Across groups, PS was higher for novel than for familiar blocks in all identified clusters: PHC (novel: mean = 0.65, SD = 0.22; familiar: mean = 0.46, SD = 0.16), ACC (novel: mean = 0.23, SD = 0.09; familiar: mean = 0.19, SD = 0.10), caudate (novel: mean = 0.22, SD = 0.09; familiar: mean = 0.18, SD = 0.07), as well as the anatomically defined hippocampus (novel: mean = 0.27, SD = 0.11; familiar: mean = 0.19, SD = 0.09), all $F_{1,38} > 6.67$, all *p*s < .014, all $\eta_p^2 > 0.15$, indicating more stable memory formation processing for novel than for familiar images.

In the PHC, losartan induced higher PS for novel and familiar blocks (novel: losartan mean = 0.75, SD = 0.19, placebo mean = 0.55, SD = 0.21; familiar: losartan mean = 0.53, SD = 0.13, placebo mean = 0.38, SD = 0.14; main effect group $F_{1,38} = 12.95$, $p < .001$, $\eta_p^2 = 0.25$) (Figure 4), indicating higher neural stability in processing both image types. There was no image condition × group interaction effect ($F_{1,38} = 1.09$, $p = .30$, $\eta_p^2 = 0.03$).

In the ACC, there was a significant image condition × group interaction effect ($F_{1,38} = 7.07$, $p = .011$, $\eta_p^2 = 0.16$), with the losartan group showing lower PS for familiar blocks compared with the placebo group (losartan mean = 0.16, SD = 0.08, placebo mean = 0.23, SD = 0.11, $t_{38} = 2.27$, $p = .03$, $d = 0.72$), but no PS difference for novel blocks (losartan mean = 0.23,

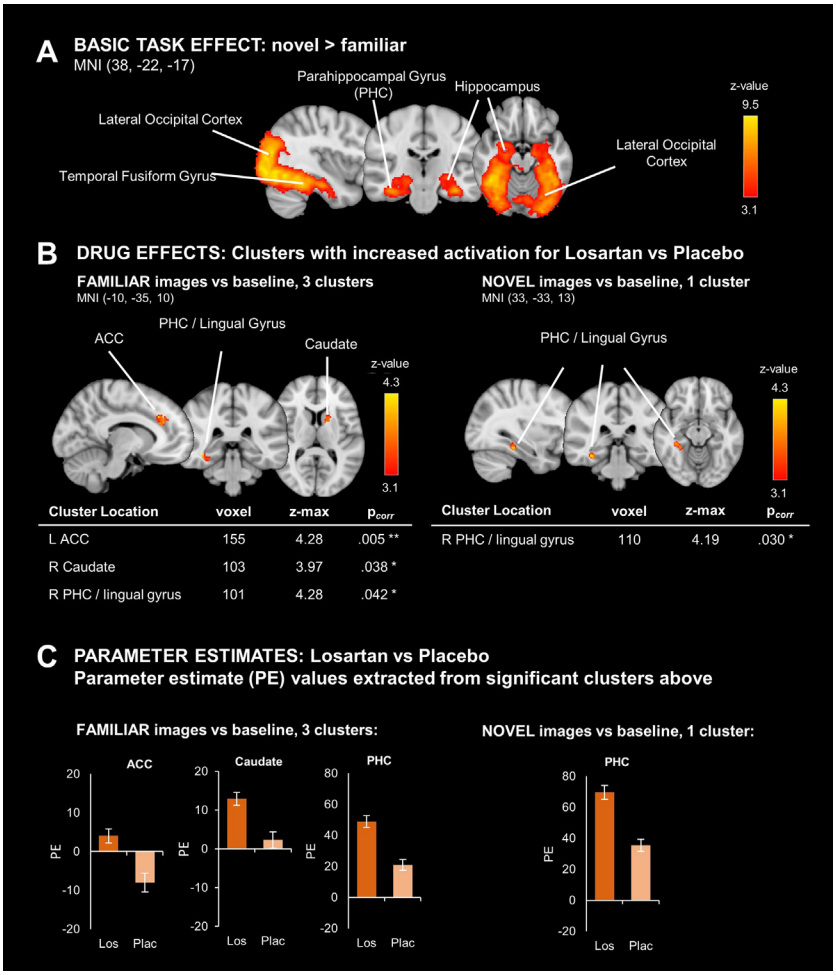

Figure 2. Univariate functional magnetic resonance imaging analyses. **(A)** Basic task effects (novel > familiar, across all 40 participants; $z > 3.1$, $p < .05$ familywise error corrected); depicted is the largest cluster from this analysis, which consists of regions from the memory network. **(B)** Depicted are the significant clusters in which the losartan [Los] group showed increased activation compared with the placebo [Plac] group, for familiar images vs. baseline (Left) and for novel images vs. baseline (Right). Statistics are based on $z > 3.1$, $p < .05$ familywise error corrected. The tables below contain additional information about the significant clusters, i.e., cluster location, cluster size in voxels, max z value, familywise error–corrected p value. *$p < .05$ corrected, **$p < .01$ corrected. **(C)** For illustrative purposes, mean parameter estimates (PEs) for each group were extracted from the significant clusters in **(B)** showing increased activation for the losartan group compared with the placebo group. Error bars represent the standard error. ACC, anterior cingulate cortex; L, left; MNI, Montreal Neurological Institute; PHC, parahippocampal gyrus; R, right.

SD = 0.09, placebo mean = 0.23, SD = 0.09, $t_{38} = -0.23$, $p = .82$, $d = -0.07$), suggesting that losartan reduced neural stability when processing already encoded familiar images (Figure 4).

There were no group differences in PS in the caudate and hippocampus (all ps $>.29$) (Figure 4).

DISCUSSION

In this study, we investigated the neural effects of ARBs on memory encoding processes that have been implicated in PTSD pathogenesis in a high-trait-anxious sample. Within the memory network, a single dose of losartan increased PHC activity in response to novel and familiar images. Outside the memory network, losartan induced higher activity for familiar images in the ACC and caudate. Additionally, losartan increased PS in the PHC in response to novel and familiar images and decreased PS in the ACC in response to familiar images. Contrary to our expectations, the drug had no effect on hippocampal BOLD response or behavioral memory recognition. However, there was a

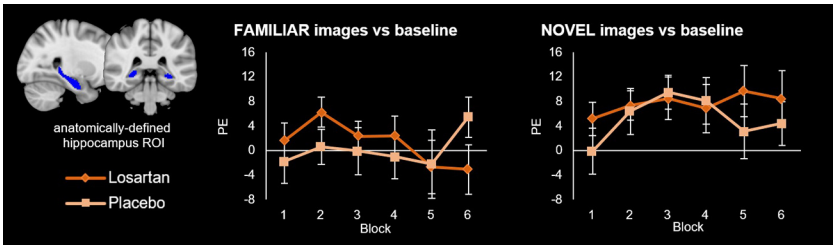

Figure 3. Hippocampus region of interest (ROI) analysis. Groups did not differ in their blood oxygen level–dependent signal over the course of the task. The parameter estimates (PEs) per block were extracted from an anatomical hippocampus mask (Harvard-Oxford cortical structural atlas).

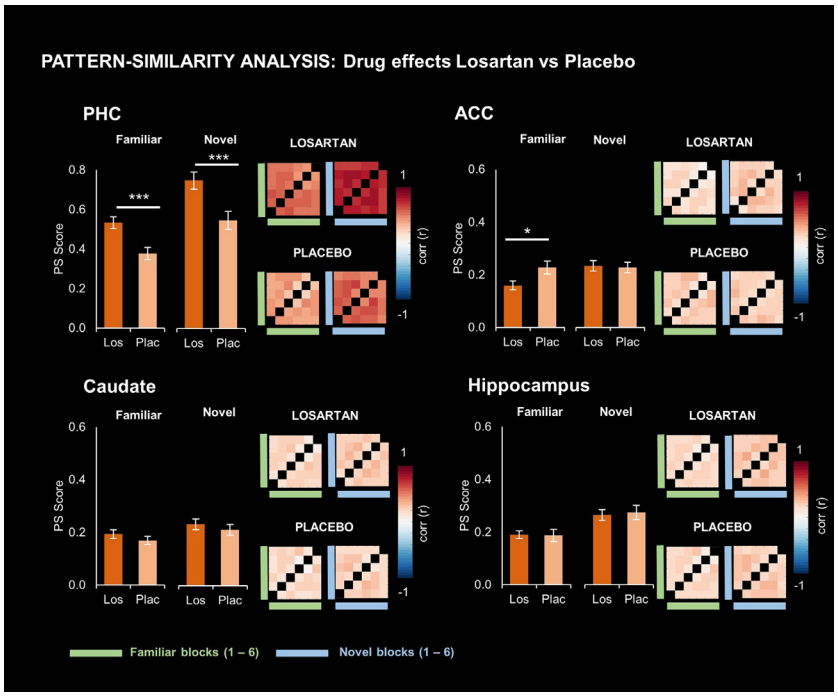

Figure 4. Multivariate pattern similarity analysis results, based on the univariate whole-brain clusters for the parahippocampal gyrus (PHC), anterior cingulate cortex (ACC), caudate, and anatomically defined hippocampus. The matrices represent the pattern similarity (PS) scores, i.e., correlated cross-voxel activity between each block, where higher correlations represent higher PS. The mean PS score was calculated for each condition (novel, familiar) and group (losartan [Los], placebo [Plac]), which is shown in the bar plots. The losartan group had greater PS for novel (blue) and familiar (green) images in the PHC. In contrast, in the ACC, the losartan group showed lower PS. No group differences were found in the caudate and hippocampus. $^{*}p < .05$, $^{***}p < .001$.

trend for losartan to facilitate visual processing of novel images.

Our findings suggest that ARBs may act on the memory system through parahippocampal rather than hippocampal modulation. While the main brain structure for memory formation is the hippocampus, it receives major input from adjacent areas, primarily the entorhinal cortices and PHC (51). These areas are important for memory formation because they modulate the sensory information that is forwarded to the hippocampus (52). The PHC is involved in processing associations between spatial, scene, and context information during memory formation (53,54) and is considered a higher-order visual processing area at the end of the ventral visual stream that particularly responds to naturalistic scenes (55–57). In turn, aberrations in these primarily higher-order visual processes have been associated with PTSD symptom development and memory intrusions (58), which are believed to be provoked by fragmented memory encoding (59).

This study proposes a new mechanism by which ARBs may counteract such higher-order sensory deficits, with potential relevance for PTSD prevention. To illustrate, losartan facilitated parahippocampal processing through enhanced BOLD activity and increased PS for both novel and familiar images. While viewing novel images demanded memory formation alongside visual processing, viewing familiar images primarily demanded visual processing, having been successfully encoded pre-fMRI. Consequently, any memory effect that was induced by losartan would have required a differential BOLD response to novel versus familiar images, which is absent in our study, consistent with a lack of losartan effects on the hippocampus or behavioral memory performance. Conversely, behavioral analyses showed a trend for the losartan group versus placebo to be faster at identifying novel images as animals/landscapes, indicating a visual processing rather than a memory encoding advantage, although this was not statistically significant. Thus, we propose that rather than directly enhancing memory formation, ARBs may primarily preserve intact memory input through improved higher-order visual processing in the PHC. This idea is supported by research showing that ARBs not only improved contextual processing of trauma-related scenes but also visual processing of negative images that had not been seen previously (7).

In addition to common univariate fMRI analyses, we employed PSA to explore more fine-graded effects of ARB action during memory formation. Previous studies have primarily used PSA on an item/trial level to understand single-item representation over time. To our knowledge, this is the first study to employ such an approach in a block design, allowing us to draw conclusions about the neural stability of a cognitive process rather than an item representation.

While univariate analyses showed that losartan induced a higher BOLD signal in the PHC, PSA further revealed that information processing in the PHC was more stable across blocks following losartan, as reflected by higher PS. Accordingly, previous research showed that greater item stability occurred during successful memory encoding in various brain regions, reflected by higher PS for stimuli presented over time (35). Because losartan had no PS effects on the hippocampus, our PSA results continued to underline that within the memory network, ARBs may particularly affect higher-order visual processing through parahippocampal modulation instead of direct hippocampal effects. Notably, our results indicate that PSA may be more sensitive to capturing targeted ARB effects on the memory network than univariate BOLD analysis: while PSA showed that neural processing was specifically more stable in the memory network (PHC), it was either less stable

(ACC) or not affected (caudate) outside the memory network. In contrast, the BOLD signal increased in clusters within the memory network (PHC) and outside the memory network (ACC, caudate). Overall, our fMRI results showed that PHC activity not only increased but also became more stable following angiotensin II receptor blockade.

In contrast to neural effects on the memory network, the lack of behavioral memory effects indicates that ARBs do not improve memory performance. Alternatively, a single dose may have initiated memory encoding effects on a neural level but was insufficient to provoke differences at a behavioral level, unlike in previous research using chronically prescribed ARBs for hypertensive treatment (5,6), including studies reporting positive memory effects in the elderly (18,19). Therefore, more chronic use of ARBs or samples with higher variability in memory performance may reveal clear behavioral memory effects.

Similarly, no group differences in memory performance between a single dose of losartan and placebo were observed in an emotional memory paradigm in a non-elderly sample (60). Instead, recognition was reduced for negative compared to neutral images within the losartan group only. This suggests that ARBs improve emotional modulation during memory formation rather than memory performance, and it is consistent with previous work showing that losartan reduced learning from negative feedback in a reinforcement paradigm (29). Similarly, we identified clusters outside the memory network in the ACC and caudate. Particularly in the ACC, functional and structural aberrations have consistently been reported in PTSD (61), while preliminary evidence highlights caudate involvement in altered reward-based decision making in PTSD (62). Together, it seems plausible that ARBs at least partially influence emotional processing or emotion-memory interactions rather than universal memory formation.

Previous work with humans has centered on examining ARB effects on fear learning and amygdala response based on encouraging rodent work showing anxiolytic (8,9), stress-reducing (63), and fear extinction–enhancing effects (64). However, direct human translation remains difficult even in well-established neurocircuits. For example, the role of the amygdala in fear conditioning is less clear in human fear responses than in rodents (65–67), while rodent models cannot fully capture the cognitive components that underlie psychiatric disease (68). In contrast, rodent work is essential for a fine-graded understanding of ARB action, such as elucidating the importance of AT_1 and AT_2 receptor interplay (69) or suggesting that the advantages of angiotensin II receptor blockade through ARBs could stem from an increased availability of angiotensin II for conversion to angiotensin IV (70–72). Angiotensin IV has been shown to improve memory formation (73,74), although the precise receptor-mediated pathways remain to be established (73,75,76). Taken together, these findings suggest that studies integrating animal and human research are necessary to advance our mechanistic and naturalistic understanding of ARB action in psychiatric disease.

The current study has some limitations. First, we cannot establish whether losartan acts directly or indirectly on the PHC, given that it remains unclear whether AT_1 receptors are expressed in the PHC or only in adjacent areas (2,77). Due to the block design, we also cannot differentiate the neural stability between correctly remembered and forgotten items using PSA. Therefore, our task may not be sensitive enough for fine-graded memory analysis by not taking advantage of PSA's full analytic potential, which may at least partially explain the lack of ARB effects on the hippocampus. In future studies, the investigators may wish to consider this during study design. Our sample being predominantly female may restrict its generalizability to the general population, but it holds increased clinical relevance due to women being more than twice as affected by anxiety disorders and PTSD than men (78,79). Additionally, sex differences are seen in RAS activity and in response to ARBs due to their role in estradiol modulation (80–83). Thus, future studies may wish to ensure adequate statistical power to assess sex effects. Furthermore, while our findings in healthy high-trait-anxious individuals cannot be translated into a PTSD population, they serve as a starting point for targeted research in which clinical studies are needed to establish the proposed effects in PTSD.

Conclusions

In summary, it is increasingly evident that the effects of ARBs on memory formation are more nuanced than initially assumed. By recruiting high-anxious rather than healthy volunteers, we have taken a step toward PTSD applicability. We extended previous work by highlighting that ARBs may act on higher-order visual processing through the PHC and propose that such an effect may facilitate intact memory input prior to consolidation, which in turn may lead to the suggested preventive effects of ARBs in PTSD development. Therefore, our results highlight the importance of exploring the role of the RAS on higher-order sensory deficits in future research.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by MQ: Mental Health Research (Grant No. MQ14F192 [to AR]) and University of Oxford Medical Sciences Internal Fund: Pump Priming (Grant No. 0003324 [to AR]). The study was also supported by the National Institute for Health and Care Research Oxford Health Biomedical Research Centre. LS is funded by the Oxford Medical Research Council Doctoral Training Partnership and the Clarendon Fund. MK is funded by the German Academic Scholarship Foundation. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health and Care Research, or the Department of Health.

MB has acted as a consultant for Jansen, the Centre for Human Drug Research, and Boehringer, has previously held shares in P1ivtal Ltd., and has received travel support from Lundbeck for attending a conference. CJH received consultancy payments from IESO digital health, Zogenix (now UCB), P1vital, and Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: The Effect of Losartan on Emotion Regulation; https://classic.clinicaltrials.gov/ct2/show/NCT05828940; NCT05828940.

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Received Oct 3, 2023; revised Nov 3, 2023; accepted Dec 14, 2023.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2023.100286.

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