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Short communication

Angiotensin receptor blockade modulates resting state functional connectivity in the memory network rather than fear network – implications for posttraumatic stress disorder

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ABSTRACT

Population-based studies have shown that the intake of Angiotensin-II receptor blockers (ARBs), commonly used to treat high blood pressure, is associated with reduced post-traumatic stress disorder (PTSD) symptoms. However, the underlying neural mechanisms remain unclear. While PTSD development is characterized by maladaptive processing within brain networks associated with fear processing and memory formation during trauma exposure, there is increasing evidence that such aberrations manifest in altered resting state functional connectivity (rsFC) of brain regions in these networks.

In this double-blind placebo-controlled study in 45 healthy volunteers with high trait-anxiety, we investigated whether the ARB losartan would affect rsFC in prominent seeds of the fear and memory network, counteracting effects seen in PTSD.

Seed selection was informed by established rsFC aberrations seen in PTSD and consisted of the hippocampus and the parahippocampal gyrus (memory network), as well the amygdala and insula (fear network).

Our results showed that a single dose of the ARB losartan decreased rsFC in the memory network from modulatory structures in the frontal cortex: losartan decreased rsFC (i) between the hippocampus and the inferior frontal gyrus involved in threat processing and memory intrusion development, and (ii) between the parahippocampal gyrus and the dorsolateral prefrontal cortex involved in top-down control. There were no drug effects on the fear network seeds. These findings may imply that ARB preserves adaptive memory function during trauma.

1. Introduction

Increasing evidence suggests that the renin-angiotensin-system (RAS) might play an important role in posttraumatic-stress disorder (PTSD) psychopathology. For example, drugs targeting the RAS, like angiotensin-II receptor blockers (ARBs), have been linked to reduced PTSD symptom development in population-based studies (Khoury et al., 2012; Seligowski et al., 2021). Research in healthy volunteers further indicates that a single-dose of the ARB losartan improves contextual information processing of highly distressing film material (Shkreli et al., 2020) – a process required for adaptive episodic memory formation during trauma (Ehlers and Clark, 2000). In addition, ARBs facilitated human fear extinction (Zhou et al., 2019), which is the core mechanism underlying exposure-based therapies – one of the most effective treatments for PTSD (Lewis et al., 2020). Such findings underscore the potential of ARBs in mitigating PTSD development and facilitating treatment. Yet, the neural underpinnings of such ARB effects are not understood.

Prominent neurocognitive theories suggest PTSD development is driven by disbalanced activity in structures associated with memory

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formation (e.g. hippocampus, parahippocampal gyrus (PHC)) and fear processing (e.g. amygdala, insula) during trauma exposure (Brewin, 2014; Brewin et al., 2010; Ehlers and Clark, 2000) – highlighting these areas as promising targets to investigate potential ARB effects on PTSD psychopathology. To illustrate, it is suggested that during trauma, amygdala and insula responses are exaggerated (Brewin et al., 2010) and cannot be sufficiently inhibited by the ventromedial prefrontal cortex (Rauch et al., 2006). This exaggerated activity impairs the contextual integration of the trauma into the episodic memory system (Brewin, 2014; Brewin et al., 2010; Ehlers and Clark, 2000) – a process linked to parahippocampal and hippocampal activity (Aminoff et al., 2013; Smith and Bulkin, 2014). As a result, cues perceptually similar to the trauma can trigger involuntary trauma memory retrieval, which underlies characteristic PTSD symptoms like memory intrusions (Ehlers and Clark, 2000). Accordingly, neuroimaging studies link PTSD to functional changes in brain areas associated with fear and memory, such as the amygdala, insula, hippocampus and the PHC (Kunimatsu et al., 2020; Liberzon and Sripada, 2007; Rauch et al., 2006), while highlighting deficiencies in the medial prefrontal cortex important for fear inhibition (Kunimatsu et al., 2020; Liberzon and Sripada, 2007; Rauch et al., 2006).

Angiotensin-II receptors are highly expressed in regions relevant to memory formation and fear processing, including hippocampus and amygdala (von Bohlen und Halbach and Albrecht, 2006). Accordingly, single-dose losartan reduced amygdala-hippocampus coupling (Xu et al., 2022) and increased parahippocampal processing (Shkreli et al., 2024) during memory tasks. Similarly, losartan facilitated discrimination of happy vs fearful facial expressions in the amygdala (Reinecke et al., 2018). Yet, only one study has examined whether ARBs more fundamentally influence the brain's intrinsic organisation, using task-independent methods such as resting state functional connectivity (rsFC). Investigating global rsFC connectivity profiles, it was shown the ARB losartan modified rsFC within the cortico-basal ganglia-thalamus circuitry, which is involved in reward, motivation, and negative emotion processing (Xu et al., 2024). However, studies investigating rsFC within core regions implicated in fear processing and memory formation are lacking, despite rsFC changes in these areas having been linked to PTSD (Jeong et al., 2019; Rabinak et al., 2011; Sheynin et al., 2020; Sripada et al., 2012). Most prominently, PTSD and posttraumatic symptom severity have been associated with increased rsFC between amygdala and insula (Jeong et al., 2019; Rabinak et al., 2011; Sripada et al., 2012), hippocampus and insula (Jeong et al., 2019) and hippocampus and inferior frontal gyrus (Sheynin et al., 2020), and decreased rsFC between hippocampus and amygdala (Sripada et al., 2012).

In this study, we aimed to investigate whether a single dose of the ARB losartan modulates rsFC within networks associated with fear processing and memory formation (hereafter referred to as 'fear' and 'memory' network for ease of communication). We expected losartan to have effects opposite to those seen in PTSD, including a reduction in rsFC within the fear network (Jeong et al., 2019; Rabinak et al., 2011; Sheynin et al., 2020; Sripada et al., 2012) and/or a reduction in rsFC between the memory network seeds and cortical structures involved in negative emotion processing (Jeong et al., 2019; Sheynin et al., 2020). We used amygdala, insula, hippocampus, and PHC seed regions, informed by established rsFC aberrations in PTSD (Jeong et al., 2019; Rabinak et al., 2011; Sheynin et al., 2020; Sripada et al., 2012) and task-based studies showing ARB effects in the hippocampus, PHC and amygdala (Reinecke et al., 2018; Shkreli et al., 2024; Xu et al., 2022). Inclusion of a PHC seed was also based on the PHC's established relevance in contextual processing (Aminoff et al., 2013) and emerging implication in the extended memory network – which includes the PHC – in PSTD psychopathology (for reviews, see Joshi et al., 2020).

2. Experimental procedures

2.1. Participants and procedure

45 healthy participants (33 women, aged 18–45 years) with high trait-anxiety (Spielberger's trait anxiety inventory (STAI-T) >40; Spielberger et al., 1970) were included following these criteria: no current DSM-IV diagnosis, >6 weeks free from CNS-active medication, BMI of 18–30, right-handed, no MRI contraindication, no first-degree relative with severe psychiatric disorder history.

After gender stratification, participants were randomly allocated to either 50 mg losartan (Cozaar, Merck Sharp & Dohme Ltd.; $n = 21$, 16 women) or matched placebo (microcrystalline cellulose; Rayotabs, Rayonex GmbH; $n = 24$, 17 women) in a double-blind design. To ensure that losartan was well-tolerated and did not influence mood, physiological symptoms or cardiovascular parameters, we assessed potential changes in subjective mood and physiological symptoms via visual analogue scale (VAS) ratings before drug administration and at drug peak time (~1hr; Lo et al., 1995), alongside heart rate and blood pressure measurements. Magnetic resonance imaging (MRI) scanning began ~1.5 hrs after drug administration. During the scan, participants were presented with a fixation cross in dimmed light instructed to keep their eyes open and to think of nothing in particular. At the end of the session, participant and experimenter guessed whether losartan or placebo was administered to ensure that double blindness was preserved.

2.2. Image acquisition

Brain imaging data was acquired for 16 participants using a 3T Siemens MAGNETOM TrioTim scanner (Oxford Centre for Clinical Magnetic Resonance Research), and for 29 participants using a 3T Siemens MAGNETOM Prisma scanner (Oxford Centre for Human Brain Activity).

Resting-state functional images were acquired a using a gradient echo EPI sequence and the following parameters: 119 × 192 × 192 field of view acquisition matrix, flip angle=89°, voxel resolution = 3 × 3 × 3.5 mm, repetition time (TR)=2000 ms, echo time (TE)=28 ms, number of volumes=180, acquisition time = 6 min 4 s. 3D high-resolution T1-weighted images were acquired using an MPRAGE sequence with the following parameters: 174 × 192 × 192 field of view matrix, flip angle = 8°, voxel resolution 1 mm^3, TR=2040 ms, TE=4.7 ms, inversion time (TI)=900 ms, acquisition time = 5 min 56 s. Field maps were acquired using a dual echo 2D gradient echo sequence with echos at TE=5.19 and TE=7.65 ms, and a repetition time of TR=500ms.

2.3. MRI data pre-processing and analysis

Imaging data was pre-processed and analysed using FSL (FMRIB Software Library; www.fmrib.ox.ac.ul/fsl).

Structural images were brain extracted using the FSL brain extraction tool 'BET'. Functional images were pre-processed in FSL using tools as follows: (i) McFLIRT for motion correction, (ii) BET for brain extraction, (iii) highpass temporal filtering using a cut-off value of 150 s (Gaussian-weighted least-squares straight line fitting, with sigma=75.0 s), (iv) B0-unwarping through the acquired fieldmap images, (v) spatial smoothing using a Gaussian kernel of 5 mm full-width at half maximum (FWHM).

To detect and remove noise components from the fMRI data, single-subject independent-component analysis was carried out using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) with an automatic dimensionality estimation. Subsequently, the identified components were automatically classified into signal and noise components using a standard training dataset within FMRIB's ICA-based Xnoiseifier (FIX) and a noise classification threshold of 20, which regresses out the signal of artefactual components reflecting non-neuronal fluctuations. Pre-processed and 'cleaned' functional data was then registered to the to the MNI standard space

using both linear (FLIRT) and non-linear (FNIRT) registration steps and optimized by the boundary-based-registration (BBR) approach

Seeds included bilateral anatomical amygdala, hippocampus, anterior PHC, posterior PHC and insula (50 % threshold, Oxford-Harvard subcortical atlas). The insula mask was split at MNI $y = 0$, to obtain the anterior part of the region (Geuter et al., 2017; Ploner et al., 2011), which has been commonly associated with PTSD (Jeong et al., 2019; Sripada et al., 2012).

For first-level FEAT analyses, one general linear model (GLM) per seed was fitted, including the regressor for the subject-specific time series, and two control regressors for temporal fluctuations related to white matter and cerebrospinal fluid. To assess group differences, whole-brain mixed-effect analyses with FLAME 1 + 2 were carried out for each seed including a voxel-wise regressor to correct for potential volumetric grey-matter differences and a regressor to correct for scanner variation ($z > 3.1$, $p<.05$ family-wise-error corrected).

2.4. Data-analysis of non-imaging variables

VAS ratings and heart rate/ blood pressure measurements were analysed using group (losartan, placebo) x time (pre-drug, peak-drug) ANOVAs. To assess whether experimenter or participants guessed drug administration above chance probability, we performed binomial tests against chance level (0.5).

3. Results

Losartan administration had no effect on heart rate, blood pressure, or subjective mood ratings (Table 1). Drug administration was not guessed above chance level by experimenter (53 % correct, p=.66) or participants (55 % correct, p=.46).

MRI analyses showed that losartan administration (vs placebo) modulated resting state functional connectivity (rsFC) of the memory network seeds (hippocampus, posterior PHC) but had no effect on fear network seed connectivity (amygdala, anterior insula). Specifically, losartan reduced rsFC between hippocampus and inferior frontal gyrus (IFG), and between posterior PHC and two clusters within the DLPFC (Fig. 1).

Table 1
Participant characteristics including group comparison of physiological measures and visual analogue scale (VAS) ratings before drug intake and at drug peak-level. VAS ratings include subjective mood and state parameters. Heart rate is presented in bpm. Systolic and diastolic blood pressure are presented in mmHg. p-values are based on the group x time interaction effect. Placebo: $n = 24$ (17 female); Losartan $n = 21$ (16 female).

	Baseline		*Drug Peak Level*		
	Placebo M (SD)	Losartan M (SD)	Placebo M (SD)	Losartan M (SD)	p
Participant Characteristics					
Age	25.00 (6.71)	21.76 (2.99)			
YOE	17.17 (3.38)	17.00 (2.41)			
STAI-T	49.83 (7.33)	46.84 (8.40)			
Physiological Measures					
Heart Rate	80 (12)	82 (12)	69 (10)	72 (12)	.63
Systolic BP	120 (16)	110 (14)	118 (13)	116 (12)	.91
Diastolic BP	73 (9)	74 (8)	72 (8)	72 (7)	.61
VAS Ratings					
Anxious	17.46 (19.28)	16.90 (20.85)	14.21 (18.69)	10.38 (15.16)	.36
Sleepy	18.21 (21.61)	16.48 (19.52)	14.75 (16.13)	17.24 (20.86)	.24
Flushed	10.04 (13.13)	20.48 (26.98)	4.96 (7.94)	12.29 (18.91)	.51
Tearful	6.08 (11.83)	8.05 (17.57)	2.42 (7.13)	3.05 (8.72)	.66
Nauseous	1.75 (2.58)	5.29 (13.72)	1.13 (1.92)	3.14 (7.13)	.47
Hopeless	7.25 (13.85)	7.76 (17.95)	6.04 (14.28)	3.86 (11.70)	.28
Tremor	2.50 (6.14)	9.62 (16.58)	1.08 (1.95)	6.33 (9.49)	.49
Sad	7.25 (14.14)	11.38 (16.86)	5.50 (12.05)	5.95 (10.48)	.08
Dizzy	2.38 (4.84)	6.67 (13.37)	4.08 (13.23)	6.62 (14.36)	.54
Depressed	6.13 (10.94)	9.29 (14.83)	4.13 (8.61)	4.81 (7.33)	.43
Heart Racing	6.75 (10.63)	13.86 (18.75)	2.83 (4.58)	7.71 (13.73)	.59
Alert	29.88 (27.43)	35.00 (26.74)	25.63 (24.75)	30.81 (26.57)	.99

Note, YOE: Years of Education; STAI-T: Spielberger's Trait Anxiety Inventory.

4. Discussion

While previous task-based neuroimaging studies showed ARB effects on the fear and memory network (Reinecke et al., 2018; Shkreli et al., 2024; Xu et al., 2022), our results suggest that single-dose losartan modulates the intrinsic organisation of structures within the memory network but not within the fear network.

Specifically, losartan decreased rsFC between hippocampus and IFG – a structure associated with threat processing (Mujica-Parodi et al., 2017; Pfeuty et al., 2015; Rahko et al., 2010) and aversive memory processing (Bourne et al., 2013; Clark et al., 2016; Kelly et al., 2007). Our results may imply that losartan reduces stronger encoding of aversive stimuli (Baumeister et al., 2001) by reducing the functional coupling between hippocampus and IFG. This finding is in line with previous research showing reduced aversive learning (Pulcu et al., 2019) and reduced negative memory (Xu et al., 2022) after single-dose losartan in healthy volunteers.

In PTSD, exaggerated fear responses during trauma are suggested to impair contextual processing and adaptive episodic memory formation (Brewin, 2014; Brewin et al., 2010; Ehlers and Clark, 2000). Moving towards a more clinical interpretation, reduced hippocampus-IFG coupling following losartan could imply that the impact of exaggerated fear responses on memory formation is reduced. This would lead to a more functional integration of trauma content into episodic memory and, ultimately, fewer memory intrusions. In line with this proposal, a previous study showed greater hippocampus–IFG rsFC in PTSD patients compared to trauma exposed controls (Sheynin et al., 2020). Further, the presence of memory intrusions has been associated with increased IFG activation in task-based studies (Battaglini et al., 2016; Bourne et al., 2013; Clark et al., 2016). Notably, this interpretation remains speculative at this point and warrants further investigation in a clinical sample.

Losartan also decreased rsFC between the posterior PHC, a higher-order visual area involved in contextual processing within the memory network, and DLPFC. The DLPFC is involved in prioritising visual information via top-down control (Blumenfeld and Ranganath, 2007; Paneri and Gregoriou, 2017; Summerfield et al., 2006). Thus, losartan may reduce coupling between visual-memory processes in the PHC and top-down executive control mechanisms in the DLPFC. Notably, preliminary evidence links greater PHC-DLPFC connectivity to higher PTSD symptom severity in a task-based functional connectivity study in assault-exposed adolescents (Cisler et al., 2013). However, since the relevance of the PHC in PTSD is only starting to emerge, direct rsFC effects between PHC and DLPFC have not been investigated. Future research is warranted to understand the full spectrum of implications.

Overall, this study provides first insight that losartan can modulate the internal organisation of core brain regions relevant for memory formation at rest, in addition to previously shown task-based effects on memory formation and emotional processing (Reinecke et al., 2018; Shkreli et al., 2024; Xu et al., 2022). Future studies need to elucidate how such findings relate to clinical outcomes, and how they could inform clinical practice. Importantly, losartan alone is unlikely to serve as an effective pharmacotherapy for PTSD (Stein et al., 2021) but may

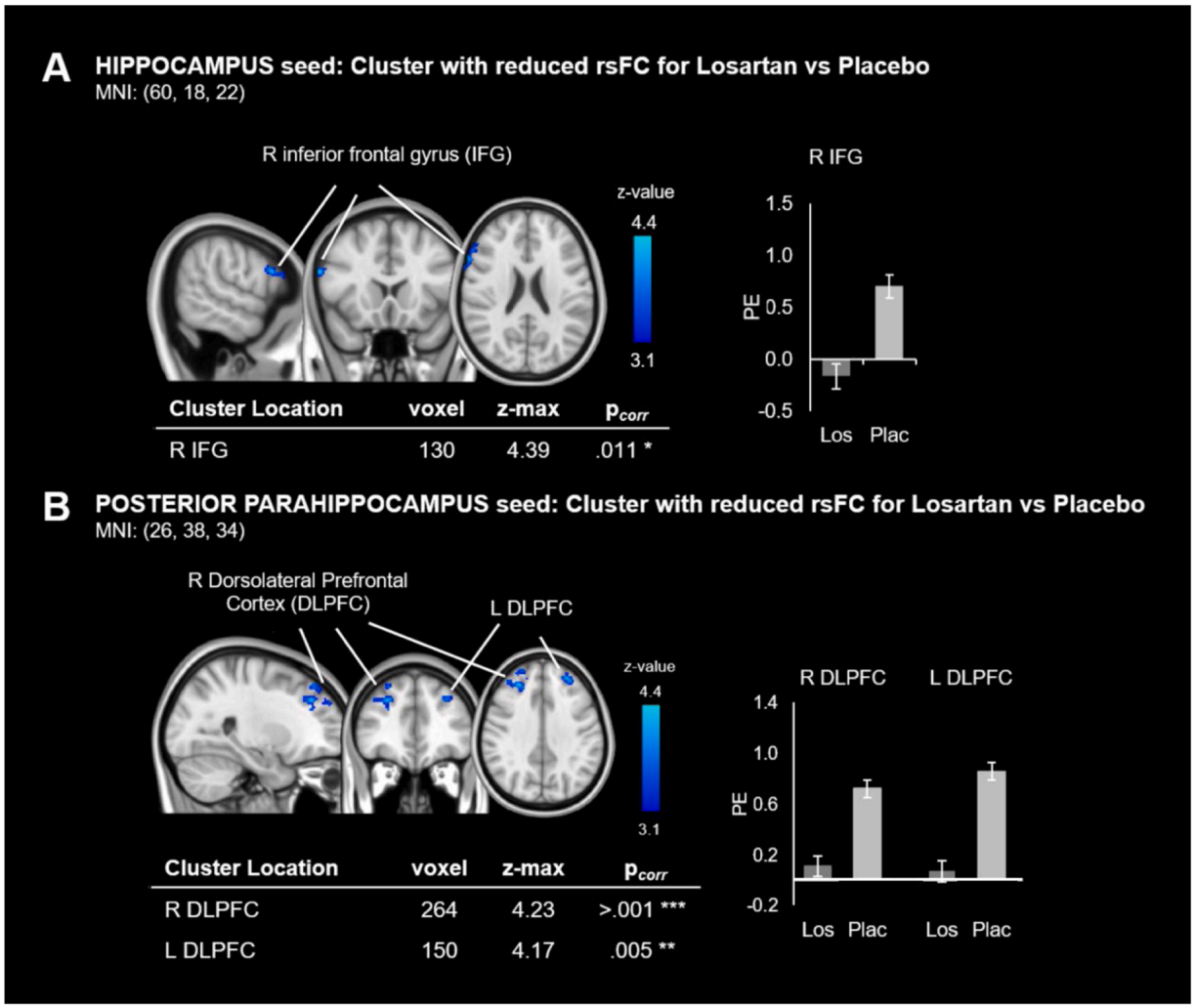

Fig. 1. Resting State Functional Connectivity (rsFC) Results. Cluster threshold $z > 3.1$ and $p<.05$, family-wise-error (FWE) corrected were used for our analyses. The tables below the brain images show additional cluster information. **A:** Compared to placebo, losartan reduced rsFC between the hippocampus and inferior frontal gyrus (IFG). For visualisation, the extracted parameter estimates are presented to the right. **B:** Compared to placebo, losartan reduced rsFC between the posterior parahippocampus and two clusters within the dorsolateral prefrontal cortex (DLPFC). For visualisation, the extracted parameter estimates are presented to the right. *$p<.05$; ** $p<.01$; *** $p<.01$.

instead be used as a complement to facilitate existing interventions such as exposure-based therapy (Zhou et al., 2019).

This study has some limitations. First, our sample consists of healthy volunteers. Although we included participants with high trait anxiety as a first step towards a more clinically relevant approach, the results need to be translated into a clinical PTSD population to examine whether ARB action remains consistent. Further, it remains to be investigated whether ARB-induced changes in rsFC translate to behavioural correlates and clinical symptoms, to ultimately establish a potential clinical use of ARBs in PTSD.

In conclusion, this study shows that acute angiotensin-receptor blockade decreases functional coupling between core structures of the memory network and fronto-cortical structures involved in threat processing and top-down control – effects opposite to those seen in PSTD. While it remains to be elucidated whether these rsFC effects of losartan manifest in behavioural correlates and clinical outcomes in PTSD, our results suggest that reducing RAS activity may help preserve adaptive memory formation.

CRediT authorship contribution statement

Lorika Shkreli: Writing – original draft, Visualization, Project administration, Formal analysis, Data curation. **Caroline Nettekoven:** Writing – review & editing, Project administration, Data curation. **Sirius Boessenkool:** Writing – review & editing, Project administration, Data curation. **Marieke Martens:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Nicola Filippini:** Writing – review & editing, Formal analysis. **Liliana Capitão:** Writing – review & editing, Supervision. **Phil Cowen:** Writing – review & editing, Resources, Funding acquisition. **Andrea Reinecke:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

None of the authors report any potential conflicts of interest.

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References

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cogn. Sci. 17 (8), 379–390.
Battaglini, E., Liddell, B., Das, P., Malhi, G., Felmingham, K., Bryant, R.A., 2016. Intrusive memories of distressing information: an fMRI study. PLoS. One 11 (9), e0140871.
Baumeister, R.F., Bratslavsky, E., Finkenauer, C., Vohs, K.D., 2001. Bad is stronger than good. Rev. General Psychol. 5 (4), 323–370.
Blumenfeld, R.S., Ranganath, C., 2007. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist 13 (3), 280–291.
Bourne, C., Holmes, E.A., Mackay, C.E., 2013. The neural basis of flashback formation: the impact of viewing trauma. Psychol. Med. 43 (7), 1521–1532.
Brewin, C.R., 2014. Episodic memory, perceptual memory, and their interaction: foundations for a theory of posttraumatic stress disorder. Psychol. Bull. 140 (1), 69–97.
Brewin, C.R., Gregory, J.D., Lipton, M., Burgess, N., 2010. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychol. Rev. 117, 210–232.
Cisler, J.M., Steele, J.S., Smitherman, S., Lenow, J.K., Kilts, C.D., 2013. Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: a network-level analysis among adolescent girls. Psychiatry Res. Neuroimag. 214 (3), 238–246.
Clark, I.A., Holmes, E.A., Mackay, C.E., Woolrich, M.W., 2016. Intrusive memories to traumatic footage: the neural basis of their encoding and involuntary recall. Psychol. Med. 46 (3), 505–518.
Ehlers, A., Clark, D.M., 2000. A cognitive model of posttraumatic stress disorder. Behav. Res. Ther. 38 (4), 319–345.
Geuter, S., Boll, S., Eippert, F., Büchel, C., 2017. Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. Elife 6, e24770.
Jeong, H., Park, S., Dager, S.R., Lim, S.M., Lee, S.L., Hong, H., Ma, J., Ha, E., Hong, Y.S., Kang, I., Lee, E.H., Yoon, S., Kim, J.E., Kim, J., Lyoo, I.K., 2019. Altered functional connectivity in the fear network of firefighters with repeated traumatic stress. Br. J. Psychiatry 214 (6), 347–353.
Joshi, S.A., Duval, E.R., Kubat, B., Liberzon, I., 2020. A review of hippocampal activation in post-traumatic stress disorder. Psychophysiology 57 (1), e13357.
Kelly, S., Lloyd, D., Nurmikko, T., Roberts, N., 2007. Retrieving autobiographical memories of painful events activates the anterior cingulate cortex and inferior frontal gyrus. J. Pain. 8 (4), 307–314.
Khoury, N.M., Marvar, P.J., Gillespie, C.F., Wingo, A., Schwartz, A., Bradley, B., Kramer, M., Ressler, K.J., 2012. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. J. Clin. Psychiatry 73 (6), 849–855.
Kunimatsu, A., Yasaka, K., Akai, H., Kunimatsu, N., Abe, O., 2020. MRI findings in posttraumatic stress disorder. J. Magnetic Resonance Imag. 52 (2), 380–396.
Lewis, C., Roberts, N.P., Andrew, M., Starling, E., Bisson, J.I., 2020. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. Eur. J. Psychotraumatol. 11 (1), 1729633.
Liberzon, I., Sripada, C.S., 2007. The functional neuroanatomy of PTSD: a critical review. In: De Kloet, E.R., Oitzl, M.S., Vermetten, E. (Eds.), Progress in Brain Research. Elsevier, pp. 151–169.
Lo, M.-W., Goldberg, M.R., McCrea, J.B., Lu, H., Furtek, C.I., Bjornsson, T.D., 1995. Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite EXP3174 in humans. Clin. Pharmacol. Ther. 58 (6), 641–649.
Mujica-Parodi, L.R., Cha, J., Gao, J., 2017. From anxious to reckless: a control systems approach unifies prefrontal-limbic regulation across the spectrum of threat detection. Frontiers (Boulder)Front. Syst. Neurosci. 11.
Paneri, S., Gregoriou, G.G., 2017. Top-down control of visual attention by the prefrontal cortex. Functional specialization and long-range interactions. Frontiers Front Neurosci. 11.
Pfeuty, M., Dilharreguy, B., Gerlier, L., Allard, M., 2015. fMRI identifies the right inferior frontal cortex as the brain region where time interval processing is altered by negative emotional arousal. Hum. Brain Mapp. 36 (3), 981–995.
Ploner, M., Lee, M.C., Wiech, K., Bingel, U., Tracey, I., 2011. Flexible cerebral connectivity patterns subserve contextual modulations of pain. Cerebral Cortex 21 (3), 719–726.
Pulcu, E., Shkreli, L., Holst, C.G., Woud, M.L., Craske, M.G., Browning, M., Reinecke, A., 2019. The effects of the Angiotensin II receptor antagonist Losartan on appetitive versus aversive learning: a randomized controlled trial. Biol. Psychiatry 86 (5), 397–404.
Rabinak, C., Angstadt, M., Welsh, R., Kennedy, A., Lyubkin, M., Martis, B., Phan, K.L., 2011. Altered amygdala resting-State functional connectivity in post-traumatic stress disorder. Frontiers Front Psychiatry 2.
Rahko, J., Paakki, J.-J., Starck, T., Nikkinen, J., Remes, J., Hurtig, T., Kuusikko-Gauffin, S., Mattila, M.-L., Jussila, K., Jansson-Verkasalo, E., Kätsyri, J., Sams, M., Pauls, D., Ebeling, H., Moilanen, I., Tervonen, O., Kiviniemi, V., 2010. Functional mapping of dynamic happy and fearful facial expression processing in adolescents. Brain Imaging. Behav. 4 (2), 164–176.
Rauch, S.L., Shin, L.M., Phelps, E.A., 2006. Neurocircuitry models of Posttraumatic stress disorder and extinction: human neuroimaging research—Past, present, and future. Biol. Psychiatry 60 (4), 376–382.
Reinecke, A., Browning, M., Klein Breteler, J., Kappelmann, N., Ressler, K.J., Harmer, C. J., Craske, M.G., 2018. Angiotensin regulation of amygdala response to threat in high-trait-anxiety individuals. Biol. Psychiatry Cogn. Neurosci. NeuroimAging 3 (10), 826–835.
Seligowski, A.V., Duffy, L.A., Merker, J.B., Michopoulos, V., Gillespie, C.F., Marvar, P.J., Stein, M.B., Ressler, K.J., 2021. The renin–angiotensin system in PTSD: a replication and extension. Neuropsychopharmacology 46 (4), 750–755.
Sheynin, J., Duval, E.R., Lokshina, Y., Scott, J.C., Angstadt, M., Kessler, D., Zhang, L., Gur, R.E., Gur, R.C., Liberzon, I., 2020. Altered resting-state functional connectivity in adolescents is associated with PTSD symptoms and trauma exposure. NeuroImage: Clinical 26, 102215.
Shkreli, L., Thoroddsen, T., Kobelt, M., Martens, M.A.G., Browning, M., Harmer, C.J., Cowen, P., Reinecke, A., 2024. Acute angiotensin II receptor blockade facilitates parahippocampal processing during memory encoding in high-trait-anxious individuals. Biol. Psychiatry Glob. Open. Sci. 4 (2), 100286.
Shkreli, L., Woud, M.L., Ramsbottom, R., Rupietta, A.E., Waldhauser, G.T., Kumsta, R., Reinecke, A., 2020. Angiotensin involvement in trauma processing—Exploring Candidate neurocognitive mechanisms of preventing post-traumatic stress symptoms. Neuropsychopharmacology 45 (3), 507–514.
Smith, D.M., Bulkin, D.A., 2014. The form and function of hippocampal context representations. Neurosci. Biobehav. Rev. 40, 52–61.
Spielberger, C.D., Gorusch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1970. Manual For the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Sripada, R.K., King, A.P., Welsh, R.C., Garfinkel, S.N., Wang, X., Sripada, C.S., Liberzon, I., 2012. Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. Psychosom. Med. 74 (9), 904–911.
Stein, M.B., Jain, S., Simon, N.M., West, J.C., Marvar, P.J., Bui, E., He, F., Benedek, D.M., Cassano, P., Griffith, J.L., Howlett, J., Malgaroli, M., Melaragno, A., Seligowski, A.V., Shu, I.W., Song, S., Szuhany, K., Taylor, C.T., Ressler, K.J., Beg, N., Sun, X., Shaikh, F., Spangler, P.T., Dempsey, C.L., Eakley, R., Kaufmann, M.L., Murphy, B.L., Merker, J., 2021. Randomized, Placebo-controlled trial of the Angiotensin receptor antagonist Losartan for posttraumatic stress disorder. Biol. Psychiatry 90 (7), 473–481.
Summerfield, C., Greene, M., Wager, T., Egner, T., Hirsch, J., Mangels, J., 2006. Neocortical connectivity during episodic memory formation. PLoS Biol. 4 (5), e128.
von Bohlen und Halbach, O., Albrecht, D., 2006. The CNS renin-angiotensin system. Cell Tissue Res. 326 (2), 599–616.
Xu, T., Chen, Z., Zhou, X., Wang, L., Zhou, F., Yao, D., Zhou, B., Becker, B., 2024. The central renin–angiotensin system: a genetic pathway, functional decoding, and selective target engagement characterization in humans. Proceed. National Acad. Sci. 121 (8), e2306936121.
Xu, T., Zhou, X., Jiao, G., Zeng, Y., Zhao, W., Li, J., Yu, F., Zhou, F., Yao, S., Becker, B., 2022. Angiotensin antagonist inhibits preferential negative memory encoding via decreasing hippocampus activation and its coupling with the amygdala. Bio. Psychiatry: Cognitive Neurosci. Neuroimag. 7 (10), 970–978.
Zhou, F., Geng, Y., Xin, F., Li, J., Feng, P., Liu, C., Zhao, W., Feng, T., Guastella, A.J., Ebstein, R.P., Kendrick, K.M., Becker, B., 2019. Human extinction learning is accelerated by an angiotensin antagonist via ventromedial prefrontal cortex and its connections with basolateral amygdala. Biol. Psychiatry 86 (12), 910–920.