Angiotensin II regulates the neural expression of subjective fear in humans

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Abstract

There has been growing interest in using pharmacological fMRI to identify novel treatments for fear, yet these models are limited with respect to determining process-specific effects on the actual subjective experience of fear which represents the key symptom why patients seek treatment. Combining a selective angiotensin II type 1 receptor (ATR1) antagonist with a fear vigilance fMRI paradigm and neurofunctional decoding in n = 87 individuals we demonstrate that AT1R blockade selectively reduces the neurofunctional reactivity to fear-inducing visual oddballs in terms of attenuating dorsolateral prefrontal activity and amygdala-ventral anterior cingulate (vACC) communication, and further show that the observed effect is due to reduced subjective fear, but not threat or non-specific negative affect, using a decoding analysis. Our findings demonstrate a highly specific role of AT1R in subjective fear experience and demonstrate the feasibility of a precision approach to the affective characterization of novel receptor targets for fear in humans.

Introduction

Anxiety disorders represent the most common mental disorder worldwide (Kessler et al., 2005) and - together with depression – have become a leading cause of disability and mortality (Correll et al., 2017; Santomauro et al., 2021). Pharmacological treatment approaches – primarily targeting monoamine and GABAergic pathways – have been established, but a considerable number of patients do not adequately respond to the anxiolytic agents or experience negative side effects (Farach et al., 2012; Insel & Wang, 2009). New treatments targeting alternative pathways to alleviate key symptoms of anxiety disorders are therefore urgently needed.

Anxiety disorders represent a heterogenous group of disorders, with separable key symptomatic and neurobiological alterations (Liu, Klugah-Brown, Zhang, Zhang, & Becker, 2021). The group of fear-related anxiety disorders (encompassing e.g. phobias and social anxiety disorders) and post-traumatic stress disorder (PTSD) is characterized by exaggerated fear responses to potential threats, hypervigilance and avoidance behavior. Animal models and experimental studies in humans suggest that these symptoms may be rooted in exaggerated threat reactivity or vigilance and an impaired ability to extinguish an acquired fear response (Becker & Zhou, 2022; Garcia, 2017; Milad, Rauch, Pitman, & Quirk, 2006). Translational models that aim at determining new treatments for fear-related disorders therefore commonly test novel compounds based on their efficacy to modulate these domains in rodent models and engage the corresponding target circuits in human pharmacological studies with concomitant functional magnetic resonance imaging (pharmaco-fMRI, Paulus & Stein, 2007). During the last decade several new target pathways have been explored, including not only classical neurotransmitter systems but also neuropeptides including e.g. the oxytocin and vasopressin and angiotensin-renin system (overview see e.g. Marvar et al., 2021; Quintana et al., 2021). More recently, accumulating evidence from different lines of research suggests that the renin-angiotensin system (Reinecke et al., 2018) – classically known for its role in the regulation of blood pressure – may represent a promising target to regulate fear (Chrissobolis, Luu, Waldschmidt, Yoakum, & D'Souza, 2020). Clinical studies have identified an important role of the angiotensin II system in stress- and anxiety-related disorders (Morrison & Ressler, 2014) and population-based studies suggest that pharmacological blockade of the angiotensin II type 1 receptor (ATR1) during trauma exposure decreases the incidence of subsequent post-traumatic fear symptoms (Seligowski et al., 2021). Experimental studies utilized the selective competitive ATR1 antagonist Losartan to demonstrate that ATR1 blockade facilitates fear extinction in rodents (Marvar et al., 2014) with subsequent pharmaco-fMRI studies in humans demonstrating that losartan has the potential to modulate threat-related amygdala functioning and circuits, including amygdala reactivity to threatening stimuli (Reinecke et al., 2018), amygdala-prefrontal connectivity during fear extinction (Zhou et al., 2019) and amygdala-hippocampal connectivity during fear memory formation (Xu et al., 2021). However, despite the important role of the extinction paradigm to map fear processing in translational models and despite the important role of the amygdala in fear processing (e.g. Janak & Tye, 2015; Mihov et al., 2013) it has become increasingly clear that the subjective feeling of fear is not accessible in rodent models and neural indices restricted to isolated brain regions are insufficient to make inferences about mental processing in humans including the subjective experience of fear (LeDoux & Pine, 2016; Woo, Chang, Lindquist, & Wager, 2017; Zhou et al., 2021). In contrast, the subjective feeling of fear is the primary reason for patients to seek treatment and effects in this domain may represent the most relevant outcome to determine the potential of novel pharmacological treatments for fear (Taschereau-Dumouchel, Michel, Lau, Hofmann, & LeDoux, 2022).

While it remains unclear whether AT1R blockade via losartan (Kessler et al., 2005) modulates fear experience in humans the conventional pharmacological fMRI approaches are of limited sensitivity to

determine process-specific modulations. The commonly applied mass univariate analytic strategies are generally characterized by low spatial and behavioral specificity (see e.g. Poldrack et al., 2017; Woo et al., 2017) and 'classical' neuroimaging indices of fear reduction such as pharmacologically attenuated amygdala reactivity have been observed during several paradigms including threat conditioning and extinction, aversive anticipation, general negative affect but also various social processes such as face processing or social sharing (e.g. Geng et al., 2018; Ma et al., 2018; Paulus et al., 2021; Xin et al., 2020). Together with studies reporting intact fear and anxiety experience in patients with complete bilateral amygdala damage (Anderson & Phelps, 2002; Becker et al., 2012; Mihov et al., 2013) and studies reporting fear and anxiety decreases in the absence of effects on amygdala activation (e.g. Diemer et al., 2017; Zhao et al., 2019; Zhou et al., 2019), these findings challenge the conventional pharmaco-fmri approach and suggest that behaviorally relevant neurofunctional indices are required to determine precise neurobehavioral profiles of neurotransmitter systems.

Against this background, the present pharmaco-fMRI study aimed to determine the specific neurofunctional effects of LT on fear vigilance by means of capitalizing on process-specific multivariate predictive neurofunctional signatures for fear and associated processes. These multivariate signatures, which have been developed to predict emotional processing, can provide larger effect sizes in brain-outcome associations as compared to local multivariate and univariate models (Kragel, Koban, Barrett, & Wager, 2018) and thus represent more precise and comprehensive brain-level descriptions of mental processes (Woo et al., 2017). Moreover, the multivariate signatures allow to access the individual mental and emotional state directly based on neurofunctional activation patterns without the need for subjective self-report. This has the advantage of avoiding meta-reflective processes which may confound the actual mental process of interest and limit ecological validity. In the current study, we, therefore, employed a number of emotional process-specific multivariate signatures to decode the effects of LT on fear-related emotional experiences, including general negative affect (Chang, Gianaros, Manuck, Krishnan, & Wager, 2015), acquired threat (i.e., conditioned fear (Reddan, Wager, & Schiller, 2018)) and subjective fear experience (Zhou et al., 2021). The combination of these decoders allowed us to test whether and which specific fear-related processes are modulated by the AT1R system. To trigger fear-related neurofunctional processes while controlling for higher-order cognitive evaluation processes we employed a visual oddball paradigm including fearful oddballs to trigger fear reactivity and vigilance as well as neutral, target, and novel oddballs to control for non-specific effects of treatment on general attention or novelty (Huettel & McCarthy, 2004). Based on accumulating evidence from animal and human studies we hypothesized that LT would reduce neural fear vigilance as reflected by attenuated neural reactivity and connectivity in the fronto-limbic fear circuitry and that this effect is related to a specific attenuation of subjective fear experience.

Method and materials

Participants

Ninety healthy right-handed participants (female = 34; age = 21.17 ± 2.12 (mean ± SD) years old) were recruited from the University of Electronic Science and Technology of China. They were free of current and past physical, neurological, or psychiatric disorders and had not taken any medication in the month before the experiment. Participants were asked to abstain from caffeine (e.g., coffee, tea, energy beverages) and alcohol the day before and on the day of the experiment. Tobacco smokers and subjects with MRI or treatment contraindications were excluded. Due to excessive movement and low performance in the oddball task, data from 3 subjects were excluded, leading to 44 LT and 43 PLC subjects for the final analyses. All participants completed written informed consent prior to participation. The experimental procedure was

approved by the local ethics committee at the University of Electronic Science and Technology of China and in accordance with the latest version of the Declaration of Helsinki. Participants received monetary compensation for study participation.

Procedures

The current study employed a randomized placebo-controlled, double-blind, between-subject pharmaco-fMRI design. Participants were randomly assigned to oral administration of either a single dose (50 mg) of LT or placebo (PLC) packed in identical capsules. An independent researcher packed and dispensed the capsules according to a computer-generated randomization list (n = 2 groups) to ensure double-blinding and randomization. The paradigm started 90 minutes after treatment administration in line with the peak plasma pharmacodynamics of the drug (Lo et al., 1995; Ohtawa, Takayama, Saitoh, Yoshinaga, & Nakashima, 1993). To control for pre-treatment differences and non-specific effects of treatment on mood and cardiovascular indices participants completed the State-Trait Anxiety Inventory (STAI) and the Positive and Negative Affect Schedule (PANAS) as well as assessments of heart rate and blood pressure at baseline, peak plasma and after the experiment (see also the experimental timeline in **Fig. 1A**).

Stimuli and oddball paradigm

A modified version of a previously validated oddball fMRI paradigm with the fearful, neutral, target, and novel oddballs was employed (Huettel & McCarthy, 2004). Participants were presented with a series of visual stimuli and 66.6% of the stimuli were neutral 'standard' images. 'Oddballs' occurred with a probability of 8.3% per oddball condition. Neutral and target oddballs employed single neutral animal pictures, the fearful oddball employed a fearful animal picture and the novel oddball used 10 neutral animal pictures with each presented once in a run. All participants completed 3 runs with 120 trials each, resulting in a total of 360 trials (240 standard trials, and 30 oddball trials for each of target, neutral, fearful, and novel stimuli). Each trial consisted of a 500 ms presentation of the picture followed by a white fixation cross on a black background with a mean interstimulus interval (ISI) of 2.7s. ISI was jittered with ± 300 ms. The order of stimuli was pseudo-randomly distributed throughout the task. Before the experiment, participants were asked to press a single button with the right index finger only when they saw the 'target oddball' during fMRI.

The stimuli for the oddball paradigm were selected from the Nencki Affective Picture System (NAPS) (Marchewka, Żurawski, Jednoróg, & Grabowska, 2014) which is a standardized set of 1356 realistic, high-quality photographs including people, faces, animals, objects, and landscapes. For the present paradigm, 34 pictures displaying animals were selected based on ratings in an independent sample (n = 60) rating the fear degree of the stimuli on a 1-5 Likert scale. We selected a stimulus with moderately higher fear and arousal induction (depicting a ferocious wolf) than the other stimuli as a fear stimulus to avoid ceiling effects. For a detailed description of the stimuli and ratings see **Supplemental Table S1**. Stimuli were presented using E-Prime stimulus presentation software (Psychology Software Tools, Sharpsburg, PA) a presented via a mirror attached to the head coil enabling viewing of projected images onto a screen positioned at the back of the MRI bore. The paradigm had a total duration of 20 minutes.

Functional MRI acquisition and preprocessing

Functional MRI data were collected using a 3.0-T GE Discovery MR750 system (General Electric Medical System, Milwaukee, WI, USA). Structural images were acquired by using a T1-weighted MPRAGE sequence (TR = 6ms; TE = 2ms, flip angle = 9°, field of view = 256 × 256 mm2; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm). Functional images were acquired using a T2*-weighted echo-

planar sequence (TR = 2000 ms; TE = 30 ms; slices = 39; flip angle = 90°; field of view = 240 × 240 mm; matrix size = 64 × 64, voxel size: 3.75 × 3.75 × 4 mm).

All images were preprocessed and analyzed using Statistical Parametric Mapping (SPM12 v7487, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The first 5 volumes of each run were discarded to allow for T1 equilibration. In line with our previous studies (Zhou et al., 2021) the remaining volumes were corrected for differences in the acquisition timing of each slice and spatially realigned to the first volume, and unwarped to correct for nonlinear distortions related to head motion or magnetic field inhomogeneity. The anatomical image was segmented into grey matter, white matter, cerebrospinal fluid, bone, fat, and air by registering tissue types to tissue probability maps. Next, the skull-stripped and bias-corrected structural image was generated and the functional images were co-registered to this image. The functional images were subsequently normalized in the Montreal Neurological Institute (MNI) space (interpolated to 2 × 2 × 2 mm voxel size) by applying the forward deformation parameters that were obtained from the segmentation procedure, and spatially smoothed using an 8 mm full-width at half maximum (FWHM) Gaussian kernel.

The first-level general linear model (GLM) included five task regressors corresponding to the 'standard', 'fearful oddball', 'target oddball', 'neutral oddball', and 'novel oddball'. For those participants who missed the target and/or pressed the button during any other conditions, we included additional task regressors to model missing and/or false alarm trials. The fixation-cross epoch served as an implicit baseline. All task regressors were convolved with the canonical hemodynamic response function and a high-pass filter of 128 seconds was applied to remove low-frequency drifts. Motion correction parameters estimated from the realignment procedure were entered as covariates of no interest.

Conventional analysis of treatment effects

We first employed mass-univariate analyses (activation and connectivity) to test LT effects on fear, neutral and novel oddballs separately. The primary analysis focused on the contrast of interest capturing fear vigilance [fearful oddball > standard], whereas the contrasts [neutral oddball > standard] and [novel oddball > standard] served to control for non-specific effects of treatment on general attention and vigilance. Based on the fronto-insular-limbic networks described in previous studies employing oddball paradigms (Huettel & McCarthy, 2004) as well as previous studies with LT reporting effects on amygdala-frontal circuits (Reinecke et al., 2018; Zhou et al., 2019) the analyses focused on these regions as defined by the Harvard-Oxford cortical and subcortical structural atlas. To this end, a single mask encompassing the anterior cingulate cortex (ACC), amygdala (Amyg), insula, middle frontal gyrus (referred to as dorsolateral prefrontal cortex (dlPFC)), inferior frontal gyrus (referred to as ventrolateral prefrontal cortex (vlPFC)) and frontal medial cortex (referred to as ventromedial prefrontal cortex (vmPFC)) (see also supplementary **Fig. 1** for the mask) was used for the correction of multiple comparisons, with a threshold of threshold-free cluster enhancement (TFCE) $p < 0.05$, family-wise error (FWE)-corrected at peak-level.

In addition to activation analysis, and in the context of previous studies demonstrating the important role of amygdala-prefrontal circuits in anxiety and early fear detection processes (e.g. Becker et al., 2012; Janak & Tye, 2015; Mihov et al., 2013) as well as in mediating some fear and negative information processing related effects of LT (Reinecke et al., 2018; Xu et al., 2021; Zhao et al., 2019) we next examined effects of treatment on amygdala functional connectivity during fear vigilance. To this end, we employed a task-based functional connectivity analysis (generalized form of context-dependent psychophysiological interactions; gPPI (McLaren, Ries, Xu, & Johnson, 2012)) with identical first-level

contrasts as the activation analyses and the bilateral amygdala from the Harvard-Oxford cortical and subcortical structural atlas (thresholded at 25% probability) as the seed region. In line with the activation analyses, we next compared the treatment groups with respect to the contrast of interest [fearful oddball > standard] using a voxel-wise comparison at the group level. Identical analyses for the contrasts [neutral oddball > standard], [novel oddball > standard], and [target oddball > standard] served to control for non-specific effects of treatment on general attention and vigilance. In line with the activation analysis, correction of multiple comparisons was restricted to the predefined mask (excluding the amygdala which served as the seed region).

Neural decoding of treatment effects on fear-related processes

We found LT specific effects on fearful, but not other, oddballs (see Results for details). However, treatment-induced changes in brain activity and connectivity do not necessarily indicate that the treatment affected the subjective fear experience. For example, given that the fearful oddball stimulus can also induce other emotional experiences (e.g., negative valence) which are inherently associated with fear the observed effect may be due to altered non-specific negative experience. We, therefore, asked whether LT has a specific effect on the fear experience. To this end, we applied three multivariate predictive models, which measured subjective fear, conditioned threat, and general negative emotion separately, to the contrasts of fearful and neutral oddballs. We used neutral oddball as a control condition here because (1) we previously demonstrated that LT had no effects on the neutral oddball (see Results for details) and (2) the neutral oddball stimulus was better matched to the fearful oddball stimulus in terms of stimulus frequency as compared to the standard stimulus. Specifically, we first used the visually induced fear signature (VIFS) (**Fig. 1B**) to predict fear experience in the different treatment groups. The VIFS has a robust generalization and high sensitivity to predict fear experience across populations, fear induction paradigms and MRI systems (Zhou et al., 2021). Inference on model performance was performed using permutation testing with 10,000 random shuffles. To test the specificity of the effects we additionally examined effects on neurofunctional signatures for related processes, in particular non-specific negative affect and threat (or conditioned fear, which is traditionally also referred to as fear). We additionally employed a picture-induced negative emotion signature (PINES) (Chang et al., 2015) designed to capture a neural activation pattern distributed across the brain that accurately predicts the level of current negative affect induced by visual stimuli, and the threat predictive signature (TPS) (Reddan et al., 2018) which was developed to accurately predict neural threat reactivity to test LT effects on conditioned threat, and general negative emotion separately (**Fig. 1C and D**). Notably, all three decoders encompassed the amygdala as a reliably predictive region (see also Chang et al., 2015; Reddan et al., 2018; Zhou et al., 2021) although emotional prediction based on the whole-brain patterns performed superior to the amygdala restricted predictions.

Statistical analysis of behavioral data

Statistical analyses of behavioral data were carried out using SPSS software (version 22; IBM Corp., Armonk, NY). Potential drug-induced changes in mood and physiological parameters were assessed using independent samples *t* tests and Bayesian *t* tests on indices collected during peak plasma. Effects on false alarms and accuracy for the target oddball were analyzed using independent samples *t* tests. All reported *p* values were two-tailed, and $p < 0.05$ was considered significant.

Results

Participants

The final sample included n = 87 (mean ± SD age = 21.17 ± 2.15 years) subjects and the treatment groups were well matched on sociodemographic parameters (LT, n = 44, 17 females; PLC, n = 43, 16 females). There were no effects of LT on non-specific emotional indices or cardiovascular activity (**Table 1**).

Behavioral indices of attention and task engagement

In order to maintain attentional engagement during the oddball task, participants were required to press a button in response to the target picture. Analyzing the number of false alarms and accuracy rate revealed that both groups showed a high task engagement and accuracy (94% or 95% accuracy, respectively), while LT did not affect this measure of basal attention (all between-group comparisons $p > 0.1$, details provided in **Table 2**).

Effects of AT1R blockade on neural fear reactivity

We initially examine general neural engagement during the task irrespective of treatment using unrestricted (whole-brain) one-sample t-tests in the entire sample. Results showed significant activation of the amygdala across all oddball contrasts (fearful oddball, neutral oddball novel oddball, and target oddball > standard; TFCE $p < 0.05$, FWE-corrected, displayed in supplementary **Figure 1**). These findings indicate that the amygdala is engaged during rare salient stimuli suggesting an engagement in the detection of salient or novel - and potentially threatening - stimuli in the environment (LeDoux & Pine, 2016). Examining treatment effects on the fear vigilance contrast [fearful oddball > standard] revealed that – relative to PLC - LT significantly reduced neural reactivity to the fearful oddball in the left dorsolateral prefrontal cortex (dlPFC; peak MNI x, y, z = -44, 20, 28; $t_{85} = -3.79$; TFCE $p = 0.04$, FWE-corrected at peak level; k = 105, **Fig. 2A**). Importantly, no treatment effect was found in other conditions (neutral oddball > standard, target oddball > standard, and novel > standard) arguing against non-specific effects treatment.

Effects of AT1R blockade on amygdala functional networks

Examination of treatment effects on fear oddball associated amygdala networks revealed that LT – relative to PLC - significantly reduced bilateral amygdala connectivity with the ventral anterior cingulate gyrus (vACC) during the fearful oddball presentation (peak MNI x, y, z = 8, 42, 16; $t_{85} = -4.00$; TFCE $p = 0.04$, FWE-corrected at peak level; k = 92, **Fig. 2B**). Further control analyses revealed that treatment did not affect amygdala functional networks during other oddball conditions (neutral oddball > standard, target oddball > standard, and novel > standard).

Process-specific effects of AT1R blockade on neurofunctional fear experience

Application of the emotion-specific neurofunctional signatures focused on predicting fearful oddballs from neutral oddballs in the separate treatment groups. Application of the VIFS capturing the level of subjective fear experience revealed significant classification performance in the PLC (accuracy = 70 ± 7.0%, binomial test $p = 0.01$) but not the LT group (accuracy = 50 ± 7.5%, binomial test $p = 1$, **Fig. 2C**). Moreover, a permutation test showed that the prediction accuracy in the LT group was significantly lower than in the PLC group (permutation test $p = 0.02$). These results suggest that the fear oddballs induced a neurofunctional representation of subjective fear experience and that this reactivity was attenuated following LT.

To further test the specificity of the LT effects on fearful oddball we applied a neurofunctional signature for unspecific negative affect (PINES). The PINES discriminated fearful vs. neutral oddballs in the LT and PLC group with comparable accuracy (accuracy = 79 ± 6.2%, binomial test $p < 0.001$, in PLC group;

accuracy = 77 ± 6.3%, binomial test $p < 0.001$, in LT group; permutation $p = 0.40$; **Fig. 2D**). These findings, together with the prediction performance of the VIFS, suggest that the fearful oddball can induce a complex array of negative emotional experiences, and LT may have specific effects on subjective fear rather than general non-specific negative affect. In addition, we applied the TPS to the data, and the result showed that TPS could not discriminate fearful vs neutral oddballs in either group (PLC: accuracy = 47 ± 7.6%, binomial test $p = 0.76$; LT: accuracy = 45 ± 7.5%; binomial test $p = 0.65$, **Fig. 2E**). These findings were in line with our previous study (Zhou et al., 2021) showing that conditioned fear and subjective fear exhibit distinct neural representations.

Discussion

Combining pharmacological fMRI with a fearful oddball paradigm and neurofunctional decoding we were able to demonstrate that transient AT1R blockade (1) selectively attenuates neurofunctional reactivity to fear-inducing visual oddballs in terms of attenuating dlPFC activation and amygdala-vACC communication, and (2) specifically reduced the process-specific neurofunctional signature response of subjective fear experience but not the representations of threat or non-specific negative affect. Together the findings indicate that the AT1R system plays a role in neurofunctional fear reactivity and fear experience and that neurofunctional signatures have the potential to improve the precision of pharmaco-fMRI for the characterization of novel receptor targets to alleviate fear.

The conventional mass univariate activation and connectivity analyses revealed that AT1R blockade specifically attenuated left dlPFC reactivity and amygdala-vACC connectivity in response to fearful oddballs. The dlPFC represents a functionally heterogenous region and has been involved in several domains related to fear processing, including implicit and explicit cognitive regulation of negative affect and task-irrelevant distractors (Beauregard, Lévesque, & Bourgouin, 2001; Delgado, Nearing, LeDoux, & Phelps, 2008; Kim & Hamann, 2007; Lévesque et al., 2003; C. Liu et al., 2021; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Phan et al., 2004; Zhuang et al., 2021) rapid attention towards salient stimuli, including threat-related stimuli (Clarke et al., 2020; Peers, Simons, & Lawrence, 2013; Sagliano, D'Olimpio, Izzo, & Trojano, 2017) and the conscious subjective experience of emotional states including fear (Kroes et al., 2019; LeDoux & Pine, 2016). In accordance with this functional characterization of the dlPFC in neuroimaging studies lesion and non-invasive brain stimulation studies have provided more causal evidence for an involvement in the fear-related process. Patients with dlPFC lesions exhibited impaired cognitive regulation of subjective fear experience (Kroes et al., 2019) while non-invasive stimulation of this region attenuates vigilance to threatening stimuli (Ironside, O'Shea, Cowen, & Harmer, 2016) and augments fear extinction (Deng et al., 2021). Likewise the amygdala, the vACC and their interaction have been extensively associated with emotional processing, such that this circuit may encode bottom-up signal indicating the presence of threat and salient information (Kober et al., 2008) which in turn informs threat acquisition (Toyoda et al., 2011) as well as the top-down regulation of emotional distractors (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006) and conditioned threat signals (Etkin, Egner, & Kalisch, 2011). Given the functional heterogeneity of the dlPFC and the amygdala-vACC pathway a corresponding interpretation of the specific functional effect of pharmacological ATR1 blockade would remain unspecific. The pattern of a treatment-induced decreased engagement in response to fearful oddballs may for instance reflect decreased automatic threat vigilance, the attenuated experience of fear or a reduced need to engage emotion regulation.

To further determine the specific effects of ATR1 blockade we therefore employed process-specific neurofunctional signatures that have been developed to precisely predict the subjective experience of fear (VIFS), general negative affect (PINES) and conditioned threat reactivity (TPS) (Zhou et al., 2021) based

on spatially distributed neurofunctional activation patterns. The VIFS and the PINES successfully discriminated fearful and neutral oddballs in the PLC group, indicating that the fearful oddball induced brain activity patterns reflecting and predictive of subjective fear and general negative affect. Treatment effects were specifically captured by the VIFS such that the subjective fear signature successfully discriminated fearful oddballs from neutral oddballs in the PLC group while ATR1 blockade abolished this discrimination suggesting reduced reactivity of the neurofunctional fear signature. In contrast, the PINES predicting non-specific negative affect successfully discriminate fearful vs. neutral oddballs in both treatment groups, suggesting that while the fearful oddballs per se did not selectively induce fear, ATR1 blockade induced fear-specific effects on the neural level. Notably, the conditioned threat signature did neither discriminate fearful vs. neutral oddballs nor treatment groups confirming a neurofunctional differentiation between conditioned threat and subjective fear experience (see e.g. also LeDoux & Pine, 2016; Zhou et al., 2021) and arguing against unspecific treatment effects.

Our findings align with accumulating evidence that suggests a role of the renin-angiotensin system and in particular of the ATR1 in fear and related processes. Previous rodent models demonstrated that targeting the renin-angiotensin system reduces indices related to fear and anxiety, such that LT-induced ATR1 blockade decreased anxiety as measured by the elevated plus-maze paradigm (Genaro, Fabris, Fachim, & Prado, 2017), abolished stress-potentiated (Marinzalda et al., 2014) and carbon dioxide-induced (Winter, Ahlbrand, & Sah, 2019) fear behavior and facilitated threat extinction while it did not affect the acquisition of a conditioned defensive threat response per se (Marvar et al., 2014). Initial studies in humans reported sustained amygdala responses to fearful faces as well as increased amygdala regulation via the medial PFC following LT (Reinecke et al., 2018; Zhou et al., 2019) with the present results suggesting a promising potential to decrease neurofunctional representations and the experience of fear.

While the current study provides initial evidence on the potential of LT to attenuate neurofunctional representations of fear future studies need to determine its potential in exaggerated fear and to evaluate its potential as an adjunct treatment to reduce and normalize the pathological fear experience. Moreover, pharmacologic blockade of the AT1 receptors with losartan may produce a complementary increase in angiotensin II levels, and subsequent work is needed to address the exact biochemical mechanisms underlying the effects observed.

In summarizing, pharmacological blockade of the AT1R attenuated the neurofunctional reactivity to fear-inducing visual oddballs in terms of attenuating dlPFC activation and amygdala-vACC communication, and specifically reduced the neurofunctional signature predictive of subjective fear. The findings reflect a functionally relevant role of the AT1R in fear experience which may serve as a promising target for novel interventions to reduce pathological fear.

Declaration of Competing Interest

The authors declare no competing interests.

Author contributions

FZ and BB designed the study; RZ and ZQ conducted the experiment and collected the data. RZ, WZ, TX, and FZ performed the data analysis. RZ, FZ, and BB wrote the manuscript draft. All authors reviewed and edited the paper.

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Table 1

Measure	Time	LT Group (n = 44)	PLC Group (n = 43)	B_{01}	P
Age (years)	/	21.55 (2.27)	20.79 (1.97)	1.35	0.10
Systolic Pressure	**Pre drug administration**	115.93(8.67)	115.35(8.90)	4.28	0.76
	Pre scanning	109.50(9.03)	110.44(9.07)	4.02	0.63
	Post scanning	114.41(8.75)	113.63(9.06)	4.15	0.68
Diastolic Pressure	**Pre drug administration**	72.93 (7.80)	70.63 (7.71)	1.93	0.17
	Pre scanning	68.89 (7.10)	67.64 (6.34)	3.28	0.40
	Post scanning	71.84 (6.00)	70.72 (8.20)	3.54	0.47
Heart Rate	**Pre drug administration**	79.52(12.48)	76.16(11.63)	2.14	0.20
	Pre scanning	70.59(10.50)	69.67 (8.41)	4.09	0.66
	Post scanning	69.59(11.10)	71.21(11.60)	3.68	0.51
STAI State Anxiety	**Pre drug administration**	38.59 (7.20)	39.30 (6.60)	4.03	0.63
	Pre scanning	36.70 (9.05)	38.39 (7.57)	3.10	0.36
	Post scanning	38.68 (8.88)	38.33 (7.66)	4.39	0.85
STAI Trait Anxiety	**Pre drug administration**	40.90 (7.81)	40.86 (7.74)	4.46	0.98
	Pre scanning	40.02 (7.45)	40.44 (7.84)	4.35	0.80
	Post scanning	40.17 (7.99)	40.88 (8.24)	4.16	0.69
PANAS Positive Affect Scale	**Pre drug administration**	16.54 (4.95)	15.44 (5.03)	2.80	0.31
	Pre scanning	14.37 (4.67)	13.49 (4.27)	3.16	0.38
	Post scanning	13.80 (4.42)	13.83 (4.97)	4.46	0.98
PANAS Negative Affect Scale	**Pre drug administration**	27.39 (5.77)	26.86 (5.67)	4.12	0.67
	Pre scanning	26.12 (6.14)	25.02 (5.62)	3.26	0.40
	Post scanning	24.88 (7.00)	24.26 (5.93)	4.11	0.67

STAI, Spielberger Trait State Anxiety Inventory; PANAS, Positive Affect Negative Affect Scale; BMI, Body Mass Index

Table 2

Measure		LT Group (n = 44)	PLC Group (n = 43)	$t_{(85)}$	P
Acc	**Target**	0.94 (0.11)	0.95 (0.08)	-0.72	0.48
False alarm	**Standard**	0.66 (0.99)	0.63 (0.08)	0.15	0.883
	Neutral	0.09 (0.99)	0.63 (0.95)	0.81	0.42
	Fearful	0.16 (0.37)	0.07 (0.34)	1.18	0.24
	Novel	0.39 (0.58)	0.56 (0.63)	-1.32	0.19

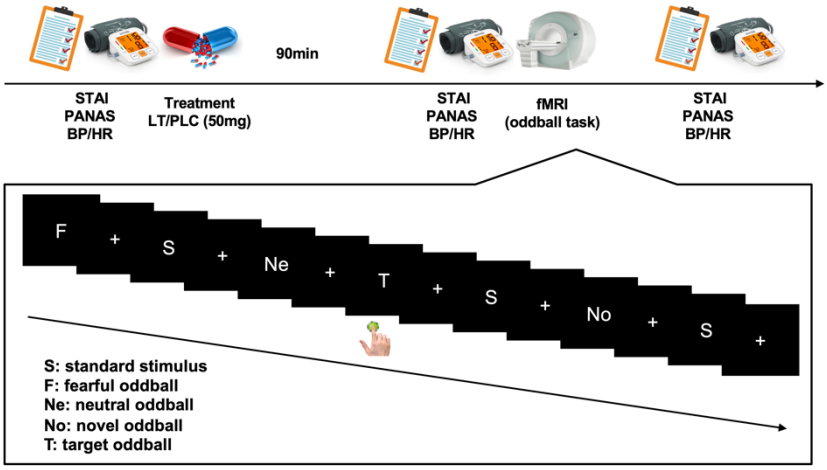
Figure legends

Fig. 1 Experimental design and neural decoding of fear-related process. (A) Experimental timeline and schematic synopsis of the fMRI task (oddball paradigm); (B) Visually induced fear signature (VIFS); (C) Threat (conditioned fear) predictive signature (TPS); (D) Picture-induced negative emotion signature (PINES). Displayed at $q < 0.001$, FDR corrected, for visual purpose.

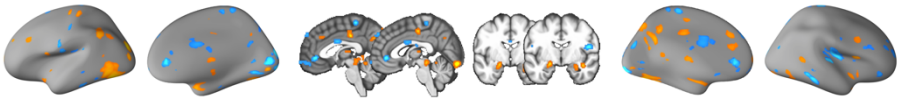
Fig. 2 Main results (A) Losartan selectively reduced dlPFC reactivity to the fearful oddball ($p < 0.05$, TFCE corrected); (B) Losartan specifically decreased functional connectivity between ACC and amygdala during the fearful oddball presentation; (C) VIFS discriminated fearful from neutral oddballs in the PLC but not the LT group and classification accuracies differed significantly between the groups (permutation test $p < 0.05$); (D) PINES discriminated fearful vs. neutral oddballs in both groups with similar accuracies. (E) TPS could not discriminate fearful vs. neutral oddballs in either group.

Fig. 1

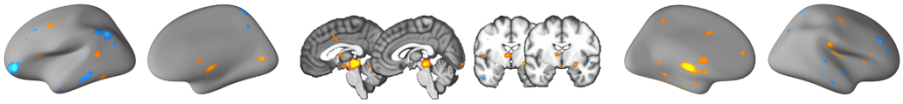
A. Experimental timeline and schematic synopsis of the fMRI task



B. Visually induced (subjective) fear signature (VIFS; q<0.001, uncorrected)



C. Threat (conditioned fear) predictive signature (TPS; q<0.001, uncorrected)



D. Picture-induced negative emotion signature (PINES; q<0.001, uncorrected)

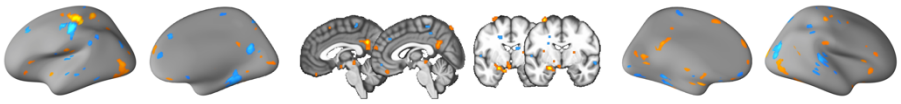
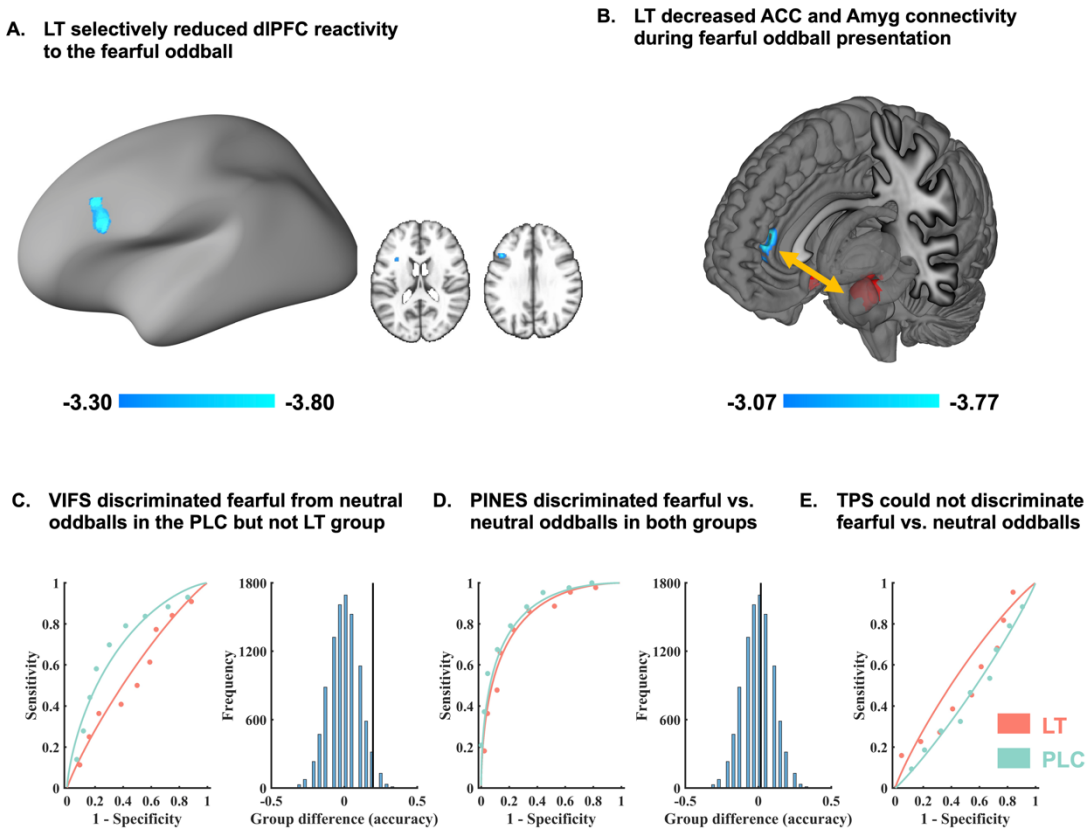


Fig. 2


A. LT selectively reduced dlPFC reactivity to the fearful oddball
-3.30
-3.80
B. LT decreased ACC and Amyg connectivity during fearful oddball presentation
-3.07
-3.77
C. VIFS discriminated fearful from neutral oddballs in the PLC but not LT group
D. PINES discriminated fearful vs. neutral oddballs in both groups
E. TPS could not discriminate fearful vs. neutral oddballs
Sensitivity
1 - Specificity
Frequency
Group difference (accuracy)
LT
PLC