Towards a Neurocognitive Understanding of Angiotensin-II Receptor Blockade: Insights into Memory, Stress, and their Implications for PTSD



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Abstract

There is increasing evidence that the renin-angiotensin-system, which is usually involved in blood pressure regulation, is relevant in posttraumatic stress disorder (PTSD) development and treatment. For example, population-based studies have shown that angiotensin-II receptor blockers (ARBs) were associated with reduced PTSD symptom development. However, the underlying mechanisms are currently not understood. In this DPhil thesis, I aim to advance the comprehension of core neurocognitive mechanisms of ARB action related to PTSD, using the most widely studied ARB 'losartan' in a series of double-blind placebo-controlled experiments. Most neurocognitive research on ARBs has focused on emotional processing and the amygdala as the brain's centre of fear. However, animal models showed that ARBs modulate hippocampal functioning, memory formation and the endocrine stress response – domains which are crucial in PTSD development. Yet, their human translation alongside supporting neuroimaging work is lacking. In the first two data chapters, I investigate memory formation and demonstrate that ARBs facilitated parahippocampal processing – a core brain region at the intersection of higher-order visual processing and memory formation. Subsequently, I investigate the brain's intrinsic organisation at rest. I demonstrate that ARBs decouple functional connectivity of regions within the memory system from regions in the frontal cortex involved in emotional processing and executive control. In my final data chapter, I focus on subjective and biological stress markers. I demonstrate that the proposed stress reducing effects of ARBs do not translate to a performance stress paradigm. Yet, exploratory analyses indicate interactions between ARB administration and hormonal contraceptive use on the cortisol stress response. Results are discussed in light of PTSD psychopathology with a particular focus on implications for re-experiencing symptoms like memory intrusions. In addition, I outline future directions for ARB research including hippocampus functioning beyond memory formation, modulatory effects of oestrogens and practical considerations for future study design.

This thesis is dedicated to my parents,

who taught me to always take life the way it comes –

with optimism, compassion and persistence!

Ju dua pafundesisht.

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In the quiet nostalgia of crafting these acknowledgements, time rewinds back to October 2019, Matriculation Day. I was excited to investigate brain plasticity markers, determined to spend some time overseas, and just ready to absorb every piece of Oxford life. What could go possibly wrong?

Little did I know that upon completion of the ethics for the FGF2 study, a tiny little virus would turn the world upside down, turning my DPhil project upside down and unfolding some of the toughest challenges to face.

But we managed to get through all of this, and I will look back and be forever grateful for this time. It has been such a privilege to experience a special place like Oxford, and it feels like so much more than academic achievement:

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My parents, Shqipe and Valon, whose story has always been my greatest inspiration. And my brother Geni, who has become a true companion. Thank you, for your unconditional love and endless support — You make every obstacle in life seem easy to overcome. Thank you, for teaching me to take joy from the small things, be grateful for everything we have, while working hard and dreaming big. I would have not made it into Oxford, if it were not for you!

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And last but not least —

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List of Abbreviations

ACC	Anterior Cingulate Cortex
ACE	Angiotensin Converting Enzyme
ACS	Attention Control Scale
ACTH	Adrenocorticotropic Hormone
AMY	Amygdala
ANG II	Angiotensin II
ANG III	Angiotensin III
ANG IV	Angiotensin IV
ARB	Angiotensin Receptor Blocker
ASI	Anxiety Sensitivity Index
AT1	Angiotensin-II Type 1
AT2	Angiotensin-II Type 2
AUC	Area under the Curve
BAS	Behavioural Activation Scale
BBR	Boundary-Based Registration
BDI	Beck Depression Inventory-II
BDNF	Brain-Derived Neurotrophic Factor
BET	Brain Extraction Tool
BIDS	Brain Imaging Data Structure
BIS	Behavioural Inhibition Scale
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
CBG	Corticosteroid-Binding-Globulin
CBT	Cognitive Behavioural Therapy
CC	Contraception
CNS	Central Nervous System
CRF	Corticotropin-Releasing Factor
CRH	Corticotropin-Releasing Hormone
CS	Conditioned Stimulus
CSF	Cerebrospinal Fluid
dlPFC	Dorsolateral Prefrontal Cortex
FWHM	Full Width at Half Maximum
GLM	General Linear Model
GM	Grey Matter
HC	Hippocampus
HGF	Hepatocyte Growth Factor
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
HRV	Heart Rate Variability
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IRAP	Insulin-Regulated Aminopeptidase
LF-HF	Low Frequency-High Frequency
LPS	Lipopolysaccharide
LTP	Long-Term Potentiation
MCFLIRT	Motion Correction FLIRT
MELODIC	Multivariate Exploratory Linear Optimized Decomposition into Independent Components
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
MVPA	Multivoxel Pattern Analysis
OCST	Oxford Cognition Stress Task
PE	Parameter Estimate
PHC	Parahippocampal Gyrus
PPA	Parahippocampal Place Area
Prim VC	Primary Visual Cortex
PS	Pattern Similarity
PSA	Pattern Similarity Analysis
PSM	Pattern Similarity Matrix
PTSD	Posttraumatic Stress Disorders
RAS	Renin-Angiotensin-System
ROI	Region of Interest
RSA	Representational Similarity Analysis

DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPI	Echo Planar Imaging
EPQ	Eysenck Personality Questionnaire
FEAT	fMRI Expert Analysis Tool
FGF2	Fibroblast Growth Factor 2
FILM	FMRIB's Improved Linear Model
FIX	FMRIB's ICA-based Xnoiseifier
FLAME	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	Functional Magnetic Resonance Imaging
fMRS	Functional Magnetic Resonance spectroscopy
FNIRT	FMRIB's Non-Linear Image Registration Tool
FPN	Frontoparietal Network
FSL	FMRIB Software Library
FWE	Family Wise Error
rsFC	Resting State Functional Connectivity
RSN	Resting State Network
SCID	Structured Clinical Interview for DSM
SN	Salience Network
SNS	Sympathetic Nervous System
STAI-S	State-Trait Anxiety Inventory-State subscale
STAI-T	State-Trait Anxiety Inventory-Trait subscale
TE	Echo Time
TFCE	Threshold-Free Cluster Enhancement
TR	Repetition Time
TSST	Trier Social Stress Test
US	Unconditioned Stimulus
VAS	Visual Analogue Scale
vmPFC	Ventromedial Prefrontal Cortex
VVS	Ventral Visual Stream

Prologue

Emma's heels echoed on the dim lit street, embracing the subtle tints of the darkening sky. The melancholic lampposts were delicately brightening the deep ruby colour of the maple leaves covered sidewalk, announcing the inevitable descent into the cold season. Her breath was visible in the chilly air, while her heart was still warmed from the hot-chocolate with her high-school friend.

She was jolted out of her thoughts, as she realized footsteps from the distance were coming closer and closer. Maple leaves rustling beneath her pace.

Within seconds, she felt a vigorous arm wrapping itself around her face, muffling her terrified scream. Her cheek rammed against the cold of the ground. Warm breath crawling down her neck. Rustling ruby red maple leaves. She was alone. Vulnerable. Her heart hammered against her rips, trying to break out in vain.

'Madam?' Emma woke from rigidity seemingly confused. An old lady had approached her looking concerned.

'Madam? Could I please use your phone to call my grandson'. She was pointing to her grocery bags a few meters away, leaning against the store's entrance.

'Oh sure, excuse my unawareness ', Emma stumbled.

Was it real or just a memory? What Emma experienced was a memory intrusion – the hallmark symptom of PTSD.

1

Chapter 1
General Introduction

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Key abbreviations

ARB: Angiotensin-II Receptor Blocker

AT1 (Receptor): Angiotensin-II Type 1

AT2 (Receptor): Angiotensin-II Type 2

PTSD: Posttraumatic Stress Disorder

RAS: Renin Angiotensin System

General Introduction

1.1. Overview

Posttraumatic Stress Disorder (PTSD) is a persistent psychiatric condition that can develop after exposure to an extremely distressing, potentially life-threating event such as physical or sexual assault, major accident, combat or natural disasters (American Psychiatric Association, 2013). PTSD is most prominently characterised by extremely vivid involuntary memories of the traumatic event called 'memory intrusions'. Other symptoms include (i) the avoidance of cues associated with the trauma, such as certain places or thoughts about the traumatic event, (ii) negative changes in mood and cognition, such as negative beliefs about the world or feelings of shame and guilt, (iii) hyperarousal symptoms, such as irritability, hypervigilance, or increased startle response (American Psychiatric Association, 2013). Most PTSD patients face psychiatric and medical comorbidities, most prominently major depression and cardiovascular disease (Boscarino, 2012; Bryant, 2019; Sareen, 2014), leading to significant personal and economic burdens, as well as pre-mature mortality (Davis et al., 2022; Sareen, 2014).

Overall, the lifetime prevalence of PTSD is 3.9 % across countries (Koenen et al., 2017). Yet, a recent meta-analysis has shown considerably higher PTSD prevalence rates of 26.5% in war survivors of countries experiencing war within the last three decades (Hoppen et al., 2021). While exposure-based cognitive-behavioural therapy (CBT) is considered one of the most effective treatments for anxiety and PTSD (Bisson et al., 2013; Lewis et al., 2020), only around half of patients achieve long-term remission, with even lower rates in comorbid depression (Springer et al., 2018). Taken together, this highlights that PTSD prevention and treatment remains a global challenge.

There is increasing evidence that the renin-angiotensin-system (RAS) might be involved in PTSD development and treatment. The RAS is a complex

endocrine system, which is predominantly involved in blood pressure regulation. However, cross-sectional population-based studies have shown that the intake of angiotensin-II receptor blockers (ARBs) is linked to reduced PTSD symptoms in trauma-exposed individuals , although the underlying mechanisms remain to be investigated (Khoury et al., 2012; Seligowski et al., 2021).

This DPhil thesis aims to advance a robust comprehension of some of the core mechanisms of ARB action relevant to PTSD, focusing on a neurocognitive perspective using task-based functional magnetic resonance imaging (fMRI) analysis, multivariate fMRI pattern similarity analysis, resting state functional connectivity analysis and examining ARB effects on the stress system.

1.2. PTSD Development – A Neurocognitive View

There are several cognitive and neurobiological theories on PTSD development. They commonly suggest that during a traumatic event neurocognitive processing is altered due to extreme stress exposure. As a result, the traumatic event is dysfunctionally integrated into the episodic memory system (Berntsen, 2009; Brewin, 2014; Brewin et al., 1996; Ehlers & Clark, 2000). Thus, PTSD theories focus on (i) the neurocircuit of fear, including classical Pavlovian conditioning and (ii) neural underpinnings of episodic memory formation. Notably, autobiographical memory and episodic memory are closely related. However, autobiographical memories also include knowledge beyond episodic memories incorporating general knowledge about oneself and one's life narrative (Rubin, 2006).

The following paragraphs will briefly cover how an ordinary episodic memory is stored, focusing on the neurocircuit of episodic memory formation, and then highlight proposed alternations during trauma

exposure due to interactions with the neurocircuit of fear. For an overview of the relevant neurocircuits in this chapter, see figure 1.1.

To begin with Emma's example from the prologue, episodic memory formation is based on an evening walk. During an ordinary evening walk continuous sensory cues – such as features of the 'ruby maple leaf' – undergo a complex hierarchical cascade along the ventral visual stream, starting with the processing of low-level perceptual information in the occipital cortex (e.g. shape, colour) to abstract high-level visual processing in the anterior temporal lobe (Kravitz et al., 2013). At the end of this cascade, the sensory cue is recognized as the object 'ruby maple leaf' (Kravitz et al., 2013). This visual information is then forwarded to the hippocampus, which receives additional multimodal sensory information about the environment, including conceptual and emotional information to be integrated and consolidated into a single memory episode (Kravitz et al., 2013; Moscovitch et al., 2016). Thus, episodic memories result in a distinct memory trace of this specific evening walk, and they include contextual details in which the 'ruby maple leaf' is encountered (e.g. evening walk through the park, on the way home, drinking hot chocolate, thinking about a conversation with a friend…). Notably, such memory traces remain dynamic and undergo continuous transformation in response to the accumulation of new experiences over lifetime (for review on episodic memory formation, see Moscovitch et al., 2016).

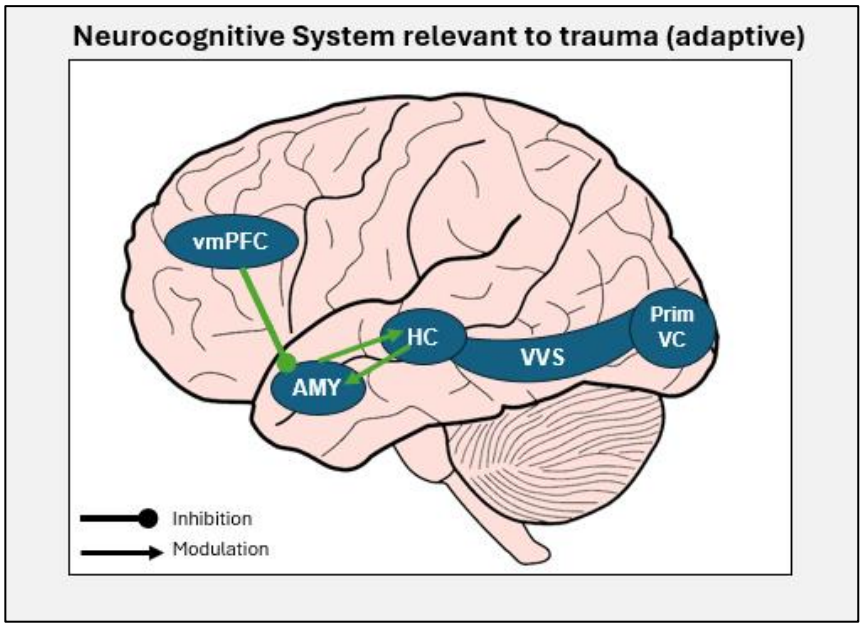


Figure 1.1 Core Network implicated in Trauma Processing and PTSD. This figure highlights the relevant brain structures implicated in PTSD pathogenesis, which will be further discussed in this thesis. During adaptive memory formation, low-level perceptual features of an object (i.e. shape or colour) are processed in the primary visual cortex (prim VC). The object continues to be processed along the ventral visual stream (VVS), in which the features become more abstract ('higher-order visual processing') for the object to be recognised, until it reaches the hippocampus (HC) to be integrated into an episodic memory. The HC and Amygdala (AMY) share reciprocal connections during memory formation and emotional processing in general. The ventromedial prefrontal cortex (vmPFC) is involved in inhibitory control of the amygdala.

It is proposed that episodic memory formation is dysfunctionally altered during trauma exposure prior to PTSD development (for a summary, see figure 1.2). Due to the extreme threat exposure caused by traumatic events, subcortical pathways are activated to rapidly project basic visual properties of the cue 'ruby maple leaf' to the basolateral amygdala, in addition to the slower cortical projections along the ventral visual stream (LeDoux, 1996; McFadyen et al., 2019; McFadyen et al., 2017; Silverstein & Ingvar, 2015). At the same time, the basolateral amygdala is highly active due to extreme threat, while top-down inhibitory control of the ventromedial prefrontal cortex (vmPFC) is suggested to be impeded (Rauch et al., 2006; Shin et al., 2006). As a result, the amygdala initiates intense fear and physiological stress

responses (through the sympathetic nervous system [SNS] and the hypothalamic-pituitary-adrenal [HPA] axis), leading to the formation of strong associations between the traumatic event and the neutral visual cue (Bremner, 2006; Goodman et al., 2012; Pitman et al., 2012). In parallel, the hippocampus first integrates sensory and contextual information tied to the traumatic experience, and then consolidates this information as a distinct episodic memory – similar to the neutral example described earlier. However, extreme stress due to trauma exposure disrupts hippocampal functioning (Bremner, 2006; Goodman et al., 2012; Pitman et al., 2012), which proposedly results in fragmented encoding of the contextual details and a non-specific representation of the traumatic event within the episodic memory system (Brewin, 2001; Brewin et al., 1996; Brewin et al., 2010). Thus, perceptually similar cues can trigger re-experiencing symptoms (Brewin, 2001; Brewin et al., 1996; Brewin et al., 2010; Ehlers & Clark, 2000). Taken together, visual cues associated with the traumatic event become powerful triggers for re-experiencing symptoms and memory intrusions. Notably, this is a simplified framework and other brain areas have been implicated in the neurocircuitry of fear response and PTSD development such as the insula and ACC (Van Elzakker et al., 2014).

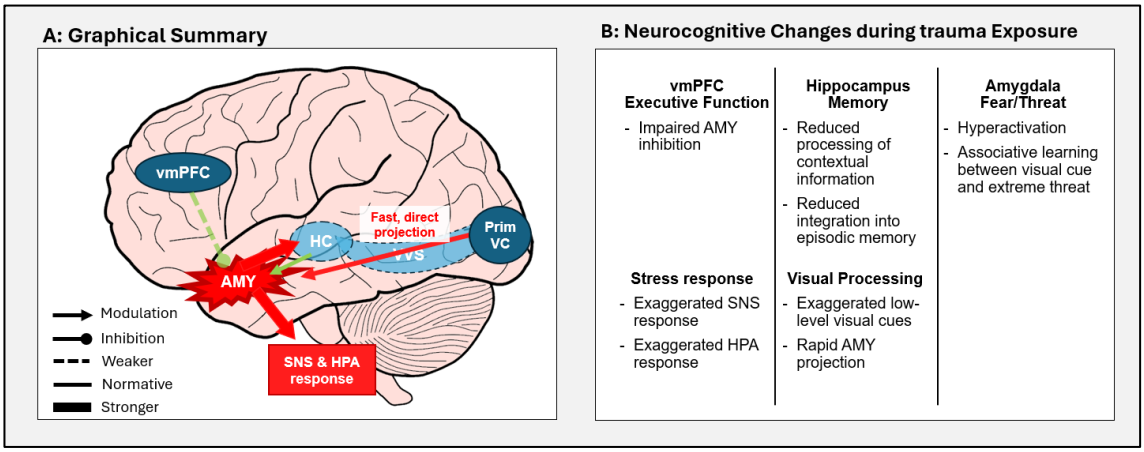


Figure 1.2. Peri-traumatic Neurocognitive Processing preceding PTSD Development. A: During trauma exposure, fast direct projections from the primary visual cortex (prim VC) reach the amygdala (AMY). At the same time, AMY activity is exaggerated building a strong association between low-level visual cues and the fear response, while its inhibition through the ventromedial prefrontal cortex (vmPFC) is impaired. Similarly, due to the traumatic stress, hippocampus (HC) functioning is impaired leading to a lack of integration of contextual information into the episodic memory trace for the traumatic event. Lighter colour represents lower activity, while red colour represents exaggerated activity. **B:** Written summary of the core neurocognitive changes during trauma exposure preceding PTSD development. VVS: ventral visual stream, SNS: sympathetic nervous system, HPA: hypothalamic-pituitary-adrenal

1.3. Cognitive and Neurobiological Manifestations of PTSD

In the previous paragraph peri-traumatic neurocognitive processes contributing to PTSD development have been outlined. Following the onset of PTSD, patients have been characterised by multifaceted neurobiological manifestations ranging from alterations in basic perceptual processing to complex cognitive functions, which will be outlined in the following paragraphs (for a summary, see figure 1.3.).

1.3.1 Ventral Visual Stream – Visual Processing

PTSD manifestation has been primarily associated with a dysfunctional fear response and/or with memory formation. However, there is increasing evidence that visual processing might play a yet underestimated role, given that memory intrusions – the hallmark symptom of PTSD – are triggered by perceptually similar cues to those encountered during trauma exposure (Ehlers et al., 2004). Most prominently this involves low-level visual details of the cue such as the colour 'ruby red' in the prologue example (Murray et al., 2022). Thus, prominent cognitive models of PTSD state that the development of memory intrusions is based on exaggerated perceptual processing of low-level visual features and sensory details (e.g. shape and colour) during trauma exposure, rather than processing high-level contextual information about the event (Ehlers & Clark, 2000).

These theoretical considerations are in line with behavioural studies showing an elevated perceptual priming response for trauma related cues in PTSD patients (Ehring et al., 2011; Kleim et al., 2012). Similarly, analogue studies in healthy volunteers exposed to traumatic (vs neutral) imagery-based stories showed that visual cues encountered prior to the traumatic stories elicited a greater priming response compared to those encountered prior to the neutral stories (Michael & Ehlers, 2007; Sündermann et al., 2013). Accordingly, enhanced perceptual priming response predicted memory intrusions (Sündermann et al., 2013). While the exact neural underpinnings involved in perceptual priming are dependent on features of the employed stimuli and task, it consistently includes attenuated brain activity in the extrastriate cortex (Badgaiyan, 2000; Nyberg, 2000), inferior frontal gyrus (Blondin & Lepage, 2005; Kim, 2017; Lee et al., 2020; Soldan et al., 2010) and higher-order visual processing areas such as the fusiform gyrus and parahippocampal gyrus (Blondin & Lepage, 2005; Lee et al., 2020; Soldan et al., 2010). Notably, these studies investigated the neural response to perceptual priming generally, i.e. without a particular focus on (analogue)

trauma exposure or PTSD. Hence, it remains to be investigated how potential alterations in such visual areas are manifested in PTSD.

To further highlight the role of visual processing in PTSD, innovative PTSD treatment approaches have been considered aiming to interfere with trauma-related visual processing – for example through playing the visuospatial video game 'Tetris' (Holmes et al., 2009). In these studies, healthy volunteers are initially exposed to highly distressing film material as an analogue to traumatic experiences. Subsequently, their memory trace is reactivated via a trauma-related cue, prior to playing Tetris to interfere with this memory. The authors yielded promising results showing that playing Tetris after encountering a trauma-related cue reduced memory intrusion development (Holmes et al., 2009; Holmes et al., 2010; James et al., 2015).

Taken together, although visual processing is often overlooked in PTSD research, there is promising evidence that it may be crucial in its psychopathology. This particularly involves a better understanding of how memory intrusions develop, and how they can be treated. In future neurocognitive studies, it is necessary to probe visual processing in patient populations to investigate potential PTSD-related aberrations and their underlying neural patterns.

1.3.2. Amygdala and Limbic System - Fear and Emotion

In contrast to visual processing, fear learning and emotional processing have been investigated extensively in PTSD – not only due to their role in PTSD pathogenesis but also their role in maintaining PTSD symptomology.

It has been consistently shown that PTSD is characterised by dysfunctional neurocognitive processing in response to threat and disruptions in regulating negative emotions (for review, see Fitzgerald et al., 2018). These cognitive manifestations are primarily rooted in the hyperactivation of core

limbic structures in PTSD, such as the amygdala, insula and dorsal ACC (for review, see Van Elzakker et al., 2014).

Given the critical role of fear learning in PTSD pathogenesis, classical conditioning paradigms have been widely studied. During fear acquisition, PTSD patients were presented with conditioned stimuli (CS) cueing either threat (CS+) followed by an aversive event (unconditioned stimulus, US), or safety (CS-). PTSD patients exhibited an increased response to both CS+ and CS-, as reflected by skin-conductance or fear-potentiated startle (Blechert et al., 2007; Glover et al., 2011). However, results on fear acquisition in PTSD have been partly inconsistent (for review, see Van Elzakker et al., 2014).

Preliminary evidence suggests that these elevated psychophysiological responses are accompanied by increased amygdala activation (Bremner et al., 2005). In addition, trauma-analogue studies using highly distressing film material as the US showed that elevated physiological response during fear acquisition was associated with the development of memory intrusions for these film clips (Streb et al., 2017; Wegerer et al., 2013).

In fear extinction, when the CS+ is not preceding the US, PTSD patients consistently exhibit deficits in updating that CS+ is no longer associated with threat through showing prolonged fear responses (Blechert et al., 2007; Milad et al., 2009; Van Elzakker et al., 2014) underpinned by increased amygdala and insula activity (Milad et al., 2009). Such fear extinction deficits potentially explain why long-term remission in PTSD remains difficult to achieve.

Similarly, PTSD patients performed more poorly in distinguishing between 'threat' and 'safety' contexts compared to healthy controls (Garfinkel et al., 2014; Jovanovic et al., 2012). This finding is consistent with experimental analogue studies demonstrating that memory intrusions occurred for visual cues associated with safety, even though these cues were not encountered during distressing film exposure (Franke et al., 2021). Such phenomena have

been interpreted as overgeneralization. Further, the impaired ability to discriminate between threat and safety cues has been proposed as a distinct biomarker for PTSD (Jovanovic et al., 2012), potentially explaining the underlying mechanism of why involuntary memories are triggered in safety contexts when exposed to trauma cues. These insights further highlight how the neurocognitive profile of PTSD is characterised by the interplay between the limbic system involved in association learning, and perceptual processing of visual cues.

Beyond fear learning paradigms, exaggerated activation in limbic structures (i.e. amygdala, insula, dorsal ACC) has been observed in PTSD patients using symptom-provocation tasks with trauma-related stimuli (e.g. Liberzon et al., 1999), as well as experimental paradigms using negative stimuli unrelated to the traumatic experience (e.g. Pannu Hayes et al., 2009; Simmons et al., 2008), (for review, see Hughes & Shin, 2011; Shin et al., 2006),(for meta-analysis, see Hayes et al., 2012).

Notably, PTSD patients exhibit greater activity in limbic structures in comparison to non-trauma exposed controls, and in comparison to trauma-exposed controls not diagnosed with PTSD (Hughes & Shin, 2011).

In addition to the functional imaging work, structural imaging work in limbic structures showed increasing evidence for smaller ACC volumes in PTSD patients (e.g. Young et al., 2018) (for meta-analysis, see Meng et al., 2014; O'Doherty et al., 2015), which might have been acquired after PTSD diagnosis (Kasai et al., 2008). In addition, there is some meta-analytic and systematic review evidence showing smaller amygdala volumes in PTSD (Ahmed-Leitao et al., 2016; Del Casale et al., 2022; Meng et al., 2014) although it was not unequivocally confirmed (O'Doherty et al., 2015). Potentially, smaller amygdala volumes are more specifically related to childhood traumatization (Ahmed-Leitao et al., 2016).

Overall, PTSD is characterised by a variety of dysfunctions in emotional processing and fear learning underpinned by hyperactivation of the limbic structures. Particularly, the deficits in threat/safety discrimination and impairments in fear extinction seem to play a dominant role in PTSD psychopathology.

1.3.3. Ventromedial PFC - Executive Control and Response Inhibition

In contrast to exaggerated activity in limbic structures, attenuated activity in executive control structures has been consistently reported in PTSD. It most prominently included attenuated activity in the vmPFC (Hayes et al., 2012; Hughes & Shin, 2011).

The vmPFC is crucial in fear learning by inhibiting amygdala response through top-down control, and by supporting hippocampal processing of contextual parameters during fear extinction (Gonzalez & Fanselow, 2020). In PTSD patients, decreased vmPFC activity has been reported during fear extinction (Milad et al., 2009; Rougemont-Bücking et al., 2011). Similarly, it has been suggested that PTSD-related impairments in distinguishing safety vs threat cues might also be underpinned by attenuated vmPFC action (van Rooij & Jovanovic, 2019).

Nevertheless, apart from inhibitory control in fear learning specifically, PTSD has been consistently linked to dysfunctional response inhibition more generally, for example in the emotional stroop paradigm (Ouhmad et al., 2023). There is ongoing discussion about PTSD-related dysfunctions in other executive control domains – such as attention control, set-shifting and working memory. Several studies report such associations, although the findings have been more heterogeneous (Aupperle et al., 2012; Polak et al., 2012; Qureshi et al., 2011). It has been suggested that this heterogeneity may result from potential PTSD sub-group effects depending on trauma-type

(e.g. war/combat vs sexual assault), gender or the presence of psychiatric comorbidities (Polak et al., 2012). Thus, it has been proposed that dysfunctional inhibitory control should be seen as the primary executive function characteristic in PTSD (DeGutis et al., 2015), while other executive dysfunctions appear to be present but less pronounced (Polak et al., 2012). With regards to structural changes, there is initial evidence of reduced vmPFC volume in PTSD patients (Kasai et al., 2008; Morey et al., 2016).

Overall, PTSD-related changes in executive functions are underpinned by attenuated vmPFC activity, which plays an important inhibitory control role in fear behaviour.

1.3.4. Hippocampus and Medial Temporal Lobe – Memory

Vivid memory intrusions are a hallmark symptom of PTSD andaberrations in memory formation and hippocampal functioning are implicated in neurocognitive theories on PTSD pathogenesis (Brewin, 2014; Ehlers & Clark, 2000). However, relatively little experimental work has directly targeted hippocampal memory functioning compared to amygdala fear response, to confirm the implications of these theories.

Prominent PTSD theories propose that dysfunctional hippocampal functioning during trauma exposure is a core element in PTSD development (Berntsen, 2009; Brewin, 2014). In this regards, the dominant clinical view is that extreme traumatic stress causes an attenuated hippocampus response, which results in fragmented episodic memory formation of the traumatic event. Therefore, perceptually similar cues are not differentiated well and can easily trigger re-experiencing symptoms like memory intrusions (Bisby et al., 2020; Brewin, 2014). However, some cognitive theories which are based on general memory retrieval, question the occurrence of fragmented memory formation during trauma exposure (Berntsen, 2009). Instead, they argue that traumatic events generate a highly detailed and strong memory

trace within the episodic memory system. They reason that episodic memory formation is enhanced for negative memories, while trauma represents an extreme form of negative memory (Berntsen, 2009). Thus - although not explicitly stated - such theories would imply elevated hippocampus activity during trauma exposure, since episodic memory encoding is dependent on hippocampal memory formation.

To support their view, behavioural studies on memory retrieval were considered to show that trauma memories are not fragmented, as proposed by clinical theories (Rubin, Deffler, et al., 2016). For instance, in one study PTSD patients and trauma-exposed controls provided narratives of their most stressful, most important and most positive memories. Using a variety of measures for memory coherence (e.g. computer algorithms, independent raters, self-reports) no consistent pattern emerged to confirm that trauma memories in PTSD patients were recalled more incoherently or fragmentedly (Rubin, Deffler, et al., 2016). However, an additional study on stressful, important and positive memories in PTSD patients and healthy controls, suggests that the retrieval mode (i.e. providing a continuous narrative vs answering detailed question about the memories) affected whether memories were rated as more or less coherent/fragmented (Taylor et al., 2020). To illustrate, a memory was rated more coherent when participants were asked to provide a continuous narrative of the event. On the other hand, when participants were asked specific questions about contextual details of the event, the memory was rated as more incoherent. Such contextual questions included for example 'What did you do just after the event? Describe what you did in enough detail that someone else would be able to imagine it accurately' or 'What were you wearing at the time of the event? Describe your entire outfit' (Taylor et al., 2020). Yet, there were no behavioural differences between PTSD patients and healthy controls. While the debate on memory fragmentation in PTSD has been continued (Brewin, 2016; Rubin, Berntsen, et al., 2016), some authors have adopted a more

nuanced perspective: They propose that the content of the traumatic memory itself is accurate (i.e. not fragmented/incoherent), but that different pieces of information about the traumatic event are stored dysfunctionally within the memory system (McNally, 2022).

Overall, the occurrence of fragmented vs non-fragmented trauma memory has been the centre of debate between different theories on PTSD development including their implications on hippocampal functioning. However, the studies informing this debate have shifted the focus on behavioural memory retrieval, which offers limited insights into the mechanisms during PTSD development requiring to investigate memory *formation* instead. Studies on memory formation, primarily in healthy volunteers and trauma-analogue samples, support the clinical view of impaired hippocampal processing. For instance, in an associative memory paradigm healthy participants were presented with either two neutral images, two negative images or a mixed image pair to be encoded (Bisby et al., 2016). At the recognition phase, participants were cued with an image from the pairs or a new image. They showed a better memory performance in recognising negative compared to neutral images ('item memory'), which was associated with higher amygdala activity for negative images at encoding. In addition, participants were also asked whether they remembered the associated image to the one they were presented ('contextual memory'). In this contextual memory part, participants performed more poorly when a negative image was involved in the pair (i.e. mixed pair or negative-negative pair), which was associated with reduced hippocampal activity at encoding. Participants achieved the best contextual memory performance in the neutral-neutral condition. Notably, such findings of improved item memory and impaired contextual memory for negative material have been replicated across studies (Anna-Maria et al., 2023; Bisby & Burgess, 2014; Ritchey et al., 2019), although they did not include neuroimaging.

Furthermore, the clinical view of fragmented memory encoding aligns with PTSD theories originating from stress research. Stress theories on PTSD development propose that stress exposure prioritises stimulus-response learning via amygdala-striatum pathways to rapidly respond to emerging threat. At the same time, hippocampus-dependent cognitive learning is compromised, which would be essential for detailed memory integration (Goodman et al., 2012; Pitman et al., 2012; Schwabe et al., 2022). In line, previous research has shown that stress exposure improved memory performance for central details of an episode but not for contextual details (Bierbrauer et al., 2021; Wiemers et al., 2013), which aligns with the neuroimaging study on item vs contextual memory presented above (Bisby et al., 2016). Similarly, studies in animal models suggest that memory encoding deteriorates under increased stress exposure (Salehi et al., 2010), which could imply attenuated hippocampal processing in humans.

Taken together, there is stronger support for the clinical view (Brewin, 2014; Ehlers & Clark, 2000) on fragmented memory integration which is in line with stress theories on PTSD-related memory formation (Goodman et al., 2012; Pitman et al., 2012; Schwabe et al., 2022). However, the fundamental limitation in all experimental studies on PTSD development is that they can merely serve as a proxy of how traumatic experiences are processed and then represented in episodic memories. While analogue studies in healthy volunteers are restricted in capturing the extent of extreme stress during trauma exposure, studies in PTSD patients cannot inform about neural processing during trauma-exposure, but only after PTSD development. Thus, it is unclear if any observed neural patterns in PTSD patients (whether elevated or attenuated hippocampal activity) might have merely developed after trauma exposure as a manifestation of PTSD, rather than being present during trauma exposure as a vulnerability or peritraumatic factor.

Apart from the debate on memory formation and hippocampal activity *during* trauma-exposure, memory impairments and hippocampal

aberrations have been consistently reported *after* trauma-exposure in PTSD patients. For example, while it has been repeatedly shown that PTSD patients exhibit impairments in fear extinction (Blechert et al., 2007; Garfinkel et al., 2014; Milad et al., 2008; Milad et al., 2009; Wicking et al., 2016), initial evidence suggests this is accompanied by decreased hippocampal activity (Milad et al., 2009). On the other hand, general episodic memory impairments have been consistently reported in PTSD (for meta-analysis, see Petzold & Bunzeck, 2022), not only in paradigms using neutral and emotional material (Brewin et al., 2007; Carrión et al., 2010; Hayes et al., 2011; Noriega et al., 2021; Samuelson, 2011), but also in more naturalistic experiments when using autobiographical memories for (neutral) everyday events (A. D. Brown et al., 2014; Schönfeld & Ehlers, 2017).

Notably, while most research in memory formation and PTSD has focused on the hippocampus, it is important to stress that memory formation is a complex process which not only depends on the hippocampus. It also includes the whole medial temporal role (MTL), most prominently the entorhinal cortex and the parahippocampal gyrus (Eichenbaum et al., 1996; Squire et al., 2015). Although these brain structures are investigated to a lesser extent compared to the hippocampus, there is preliminary evidence of PTSD-related alternations in these brain structures as well (Kunimatsu et al., 2020; Sakamoto et al., 2005).

Apart from the functional work, structural work has repeatedly indicated smaller hippocampal volumes in PTSD patients. In fact, among all structural alterations associated with PTSD, reductions in hippocampal volume have been reported most consistently (for meta-analysis, see Logue et al., 2018; O'Doherty et al., 2015) and there is ongoing debate from twin-studies in combat veterans whether smaller hippocampi might be a risk factor for PTSD development (Bremner et al., 2021; Gilbertson et al., 2002). Apart from the hippocampus, volume reductions in other areas of the medial temporal

lobe have been reported, such as the parahippocampal gyrus (Crombie et al., 2021).

In summary, although relatively little brain-imaging work has directly probed neurocognitive theories on PTSD pathogenesis involving memory and the hippocampus, there is accumulating evidence that functional impairments and structural changes are present in various domains. That is, PTSD patients are characterised by impairments in memory function and attenuated hippocampal activity (at least after PTSD development). Thus, it seems plausible that during trauma-exposure hippocampal processing was impaired, particularly since smaller hippocampal volumes have been implicated as a risk factor for PTSD development (Gilbertson et al., 2002). However, unless there is direct neuroimaging work probing theories on PTSD pathogenesis, the role on the hippocampus remains to be confirmed. Nevertheless, the minimal consensus among opposing theories is that hippocampus processing during trauma exposure is dysfunctional – whether due to attenuated hippocampus processing and fragmented memory formation or elevated hippocampus processing and exaggerated memory formation.

1.3.5. Stress – A Key Modulator in PTSD

Beyond neural underpinnings, a core precipitating and modulating factor of PTSD is the stress response, which not only directly influences cognitive functioning but also introduces an additional layer of complexity to the understanding of PTSD psychopathology.

The bodily stress system consists of two distinct yet interconnected systems. On the one hand, there is the sympathetic nervous system (SNS) which is rapidly activated during acute stress (Goldstein, 1987). It is primarily responsible for a quick physiological and physical response to threat, and it initiates the 'fight or flight' reaction (Jansen et al., 1995). Once acute stress has

passed, SNS activity ceases. On the other hand, there is the hypothalamus-pituitary-adrenal (HPA) axis, which includes an endocrinal cascade beginning with the release of corticotropin-releasing hormone (CRH) in the hypothalamus, followed by adrenocorticotropic hormone (ACTH) release in the pituitary gland, to the secretion of the end product cortisol in the adrenal gland (Herman et al., 2016; Smith & Vale, 2006). In contrast to the SNS, the HPA-axis responds to both acute and chronic stress, and operates more slowly. It is primarily responsible for a sustained stress response to adapt to prolonged and chronic stress exposure, and to maintain homeostasis (Herman et al., 2016; Smith & Vale, 2006). Thus, the HPA axis remains active for a prolonged period of time, and it modulates metabolic function, inflammation and immune system processes (Bellavance & Rivest, 2014; Dunn, 2007; Pasquali et al., 2006).

Within both systems, the stress response is underpinned by neuroactive stress hormones, such as adrenaline and noradrenaline in the SNS (Goldstein, 1987; Jansen et al., 1995), or glucocorticoids such as cortisol in the HPA-axis (Herman et al., 2016; Smith & Vale, 2006). In studies investigating the HPA-axis, the measurement of stress hormones remains the primary marker of HPA-functioning for both animal and human research (Bali & Jaggi, 2015). In contrast, SNS research in humans most commonly includes physiological indicators, such as heart rate, heart rate variability and electrodermal activity (Bali & Jaggi, 2015), while animal research more commonly includes endocrine assessment of adrenaline and noradrenaline (e.g. Klimeš et al., 2005; Sueta et al., 2014), as well as direct sympathetic nerve activity measurements (e.g. Stocker & Muntzel, 2013).

PTSD-related changes have been observed in both stress systems. Typically, SNS response is upregulated in PTSD, leading to common noradrenergic mediated symptoms such as increased startle response, elevated heart rate and hyperarousal (O'Donnell et al., 2004; Park et al., 2017; Pole et al., 2009). Moreover, elevated physiological responses can serve as a marker of fear

generalisation (Ehlers et al., 2010; Suendermann et al., 2010). In these studies, it was shown that elevated heart rate to general trauma reminders one month after trauma exposure predicted future PTSD symptom severity in motor vehicle accident survivors and physical assault survivors (Ehlers et al., 2010; Suendermann et al., 2010).

With regards to the HPA-axis and PTSD, studies on cortisol secretion have shown a nuanced pattern of effects: While in the direct aftermath of the traumatic event cortisol levels are elevated, this prompts a rebound effect in the long-term, leading to attenuated cortisol levels when the traumatic event becomes more distal (Steudte-Schmiedgen et al., 2016).

Since neuroactive stress hormones modulate neurocognitive functioning, they may have important implications for PTSD pathogenesis and its associated neurocognitive alterations. For example, previous work has shown that stress enhances memory encoding for information presented during and immediately after stress exposure, potentially through adrenaline/noradrenaline modulation in the SNS (Schwabe et al., 2012; Vogel & Schwabe, 2016). Conversely, memory encoding is reduced for information presented shortly after stress exposure (i.e. ~30min after) due to glucocorticoid action (Schwabe et al., 2012; Vogel & Schwabe, 2016). From a PTSD psychopathology perspective, this may explain why PTSD patients remember specific details during the traumatic memory very precisely, while context information before or after trauma exposure is only poorly retained.

In addition, neuroactive stress hormones exhibit strong interactions with amygdala and hippocampal functioning. In the amygdala, there is reciprocal modulation with the HPA-axis. While the HPA axis regulates amygdala function and fear behaviour, the amygdala stimulates HPA-axis activity (Davis & Shi, 1999; Feldman et al., 1995; Zhang et al., 2018). For example, in animal studies it was shown that fear response was increased when

corticosterone, the animal equivalent to human cortisol, was chronically administered into the amygdala over seven days (Myers et al., 2005). Further, chronic stress increased corticotropin releasing factor (CRF) expression in the amygdala, which is the key hormone initiating the signalling pathway and hormone cascade in the HPA-axis (Shekhar et al., 2005).

With regards to the hippocampus, it has been shown that prolonged glucocorticoid action impairs hippocampal functioning and synaptic plasticity (Alfarez et al., 2003; Krugers et al., 2006; Myers et al., 2014; Suri & Vaidya, 2013; Wosiski-Kuhn et al., 2014), which might underlie PTSD-related impairments in memory function and fear extinction. Notably, it is suggested that glucocorticoid action on hippocampal functioning follows and inverted U-function (de Quervain et al., 2017). That is, moderate glucocorticoid levels are required for optimal hippocampal functioning, while attenuated and elevated glucocorticoid levels have been linked to memory impairments (de Quervain et al., 2017).

Taken together, the important modulatory role of the bodily stress response highlights that the SNS and HPA-axis including their neuroactive hormones are important to consider in neurocognitive PTSD research.

To conclude, it becomes evident that PTSD manifestation encompasses a complex interplay of interconnected neurocognitive processes, including perceptual processing, emotional processing, fear learning, executive function and memory, while being modulated by the bodily stress systems.

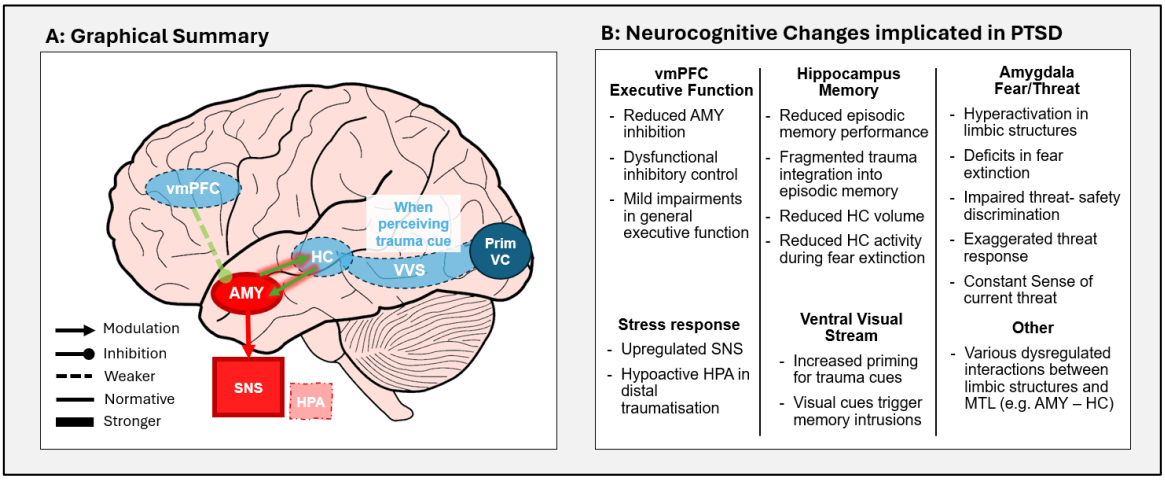


Figure 1.3. Summary of neurocognitive changes after PTSD development. A: Lighter colour represents lower activity. Red colour represents exaggerated activity. The red-framed arrows between the amygdala (AMY) and hippocampus (HC) indicate that interaction between those two brain regions is dysregulated. Since perceptually similar cues to the traumatic experience ca trigger memory intrusions, processing within the ventral visual stream (VVS) is likely impaired. **B:** Written summary of the core neurocognitive changes after PTSD development. The list is not exclusive. vmPFC: ventromedial pre-frontal cortex, VVS: ventral visual stream, SNS: sympathetic nervous system, HPA: hypothalamic-pituitary-adrenal, prim VC: primary visual cortex

1.4. Redefining the Renin-Angiotensin System: A Novel Target for PTSD?

There is a growing body of research showing that drugs targeting the renin-angiotensin-system modulate neural response, emotional processing, and cognition. These drugs most notably include angiotensin-receptor-blockers (ARBs), the first-line treatment for hypertension (Terry et al., 2012). Particularly, population-based studies have shown that trauma-exposed individuals who routinely took ARBs (i.e. for hypertensive treatment) were less likely to exhibit PTSD symptoms (Khoury et al., 2012; Seligowski et al., 2021). While this finding suggests that ARBs may contribute to PTSD prevention, the neurocognitive underpinnings remain unclear. Thus,

exploring the renin-angiotensin system (RAS) offers a new target for PTSD pathophysiology and potential preventative and therapeutic insights.

1.4.1 The Renin-Angiotensin-System – A General Overview

The Renin-Angiotensin System (RAS) is a complex endocrine pathway primarily involved in the regulation of blood pressure, blood volume, and electrolyte balance in the body to maintain cardiovascular homeostasis (see figure 1.4. for overview). In brief, the RAS acts through a negative feedback loop starting from renin release stimulating an enzyme cascade resulting in angiotensin-II release, which in turn initiates vascular changes to maintain homeostasis resulting in renin inhibition (Atlas, 2007; Peach, 1977).

In detail, disturbances in homeostasis (e.g. low blood pressure, low blood volume, low sodium levels) initiate the release of renin from the juxtaglomerular cells in the kidneys. Renin cleaves the inactive precursor angiotensinogen in the bloodstream to form angiotensin-I, which is then converted to angiotensin-II by angiotensin-converting enzyme (ACE). Via various enzyme reactions, angiotensin-II is subsequently converted to Angiotensin(1-7) and angiotensin-III, followed by angiotensin-III to angiotensin-IV conversion (Atlas, 2007; Peach, 1977).

Angiotensin-II is the potent molecule of the RAS, which initiates vasoconstriction and sodium retention resulting in increased blood pressure. Further, it stimulates the adrenal glands to release aldosterone, which itself initiates increased blood pressure through blood volume enhancement. In turn, the increase of blood volume regulated by angiotensin-II and aldosterone is detected by the juxtaglomerular cells in the kidneys which subsequently inhibit renin release (Atlas, 2007; Peach, 1977).

Importantly, physiological and psychological stress also activates the RAS by stimulating renin release, leading to increased angiotensin-II levels through the endocrine cascade described above (Atlas, 2007). Apart from direct effects on the RAS, angiotensin-II has been shown to influence cell proliferation, oxidative stress and pro-inflammatory response (Benigni et al., 2010; Escobar et al., 2004; Ji et al., 2016; Wolf & Wenzel, 2004). Taken together, previous work highlights the role of the RAS in psychophysiological functioning, which warrants detailed investigation.

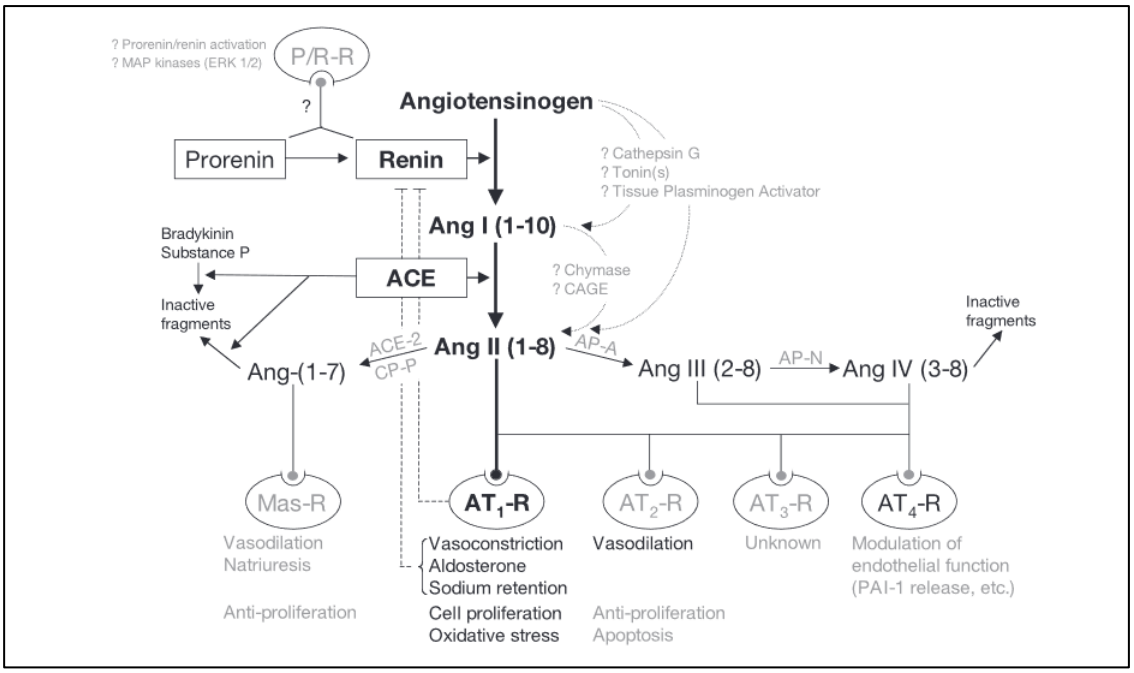


Figure 1.4. Overview of the renin-angiotensin-system (RAS). Reproduced from Atlas, 2007. Note, that newer studies have shown that angiotensin-III can also bind to angiotensin-II receptors (Wright et al., 2008), as will be described in the next paragraphs. Ang II: Angiotensin-II; Ang III: Angiotensin III, Ang IV: Angiotensin IV.

1.4.2 Receptors in the Renin-Angiotensin-System

In the RAS there are two main angiotensin-II receptors: Angiotensin-II type 1 (AT1) receptors and angiotensin-II type 2 (AT2) receptors. The AT1 receptor is mainly involved in angiotensin-II action, such as vasoconstriction, pro-inflammatory response, and aldosterone release. It is highly expressed in the cardiovascular system compared to the AT2 receptor (Hernandez Schulman

et al., 2007). On the other hand, AT2 receptors are believed to counteract the effects of AT1 receptors (Hernandez Schulman et al., 2007; Horiuchi et al., 1999; Yang et al., 2012), although their role is generally less well understood. Similarly, angiotensin-III can also bind to both AT1 and AT2 receptors, complementing their functioning in RAS homeostasis (Wright et al., 2008).

Angiotensin 1-7 binds to the C-MAS receptor and is involved in vasodilation and improved cardiovascular function via counteracting angiotensin-II mediated effects (Medina & Arnold, 2019; Santos et al., 2003).

Angiotensin-IV binds to specific angiotensin-IV receptors, although there is ongoing discussion on the function of these receptors (Vanderheyden, 2009). While some research suggests that angiotensin-IV receptors are insulin-regulated aminopeptidase (IRAP) receptors (Albiston et al., 2001; Albiston et al., 2003; Gard, 2008), other studies propose they are the hepatocyte growth factor (HGF) receptors named c-Met (Wright et al., 2008).

1.4.3. Discovery of a Renin-Angiotensin-System in the Brain

Apart from the peripheral RAS, a central RAS has been discovered in the 1960s and 1970s (Bickerton & Buckley, 1961; Ganten et al., 1971; Reid, 1977), which involves the local synthesis of proteins and enzymes involved in the RAS cascade, such as renin, ACE and angiotensin peptides (Ganten & Speck, 1978; Hermann et al., 1987).

While it has initially been suggested that the role of the central RAS, including the role of angiotensin-II, mirrors their peripheral action in vasoconstriction and blood pressure regulation (Bickerton & Buckley, 1961; Ganong, 1977; Reid, 1977), it soon became apparent that central effects extend beyond the peripheral functions. In this regards, early findings on central angiotensin-II action have been derived from rodent models in the 1980s-1990s showing that increased angiotensin-II secretion induced anxiety-like behaviour and impaired memory function (Barnes et al., 1989). Shortly after,

promising results were published demonstrating that that ARBs mitigate such impairments, by reducing anxiety-like behaviour and improving memory formation (Barnes et al., 1990; Dennes & Barnes, 1993; Kaiser et al., 1992; Raghavendra et al., 1998), but see (Shepherd et al., 1996), pioneering a new area of research.

Subsequently, the syntheses of renin and angiotensinogen in proximity, which are required to initiate the RAS cascade, have been shown in brain areas relevant for psychopathology, such as in the amygdala (central nucleus), hippocampus (CA1-3 region) and the bed nucleus of the stria terminalis (Lavoie et al., 2004). Similarly, receptors for angiotensin-II, the potent metabolite of the RAS, are expressed throughout the brain, including areas within the PTSD neurocircuit like hippocampus, amygdala and pre-frontal cortex (von Bohlen und Halbach & Albrecht, 2006) making them a particularly promising target of research in psychiatric disease.

Over the past decade, animal research on the RAS and on neural ARB effects has been steadily growing. While the direct anxiolytic effect of ARBS have been repeatedly replicated (de los Angeles Marinzalda et al., 2014; Genaro et al., 2017; Llano López et al., 2012) but see (Marvar et al., 2014) , increasing effort has been made to understand their underlying mechanism. In this regards, previous research has focused on neurocognitive processes and neural underpinnings relevant in anxiety and PTSD, most notably amygdala functioning (de los Angeles Marinzalda et al., 2014), fear extinction (Marvar et al., 2014) and stress response (Armando et al., 2007; Wincewicz et al., 2016). Yet, translational work in humans is only gradually expanding, with neuroimaging work remaining sparse.

1.5. Neurocognitive Effects of Angiotensin Receptor Blockers

In alignment with the elaboration of peri-traumatic neurocognitive processing described in chapter 1.2. and neurocognitive manifestations after PTSD onset described in chapter 1.3., the following paragraphs highlight the domains in which ARB effects have been observed focusing on visual processing, fear learning, emotional processing, executive control, memory formation and stress. Key findings have been summarised in figure 1.5.

1.5.1. The Effect of ARBs on Visual processing

Since most research on neural ARB effects has been conducted in rodents, results in visual processing are sparse, if not completely absent. While there is no neural study investigating visual processing in response to ARBs in neither animals nor humans, it has been shown in a behavioural study that a single dose of 50mg losartan (vs placebo) facilitated the identification of the contents of blurry negative images in healthy volunteers (Shkreli et al., 2020).

1.5.2. The Effect of ARBs on Fear Learning and Fear Extinction

Given the crucial role of fear response in PTSD, fear learning and fear extinction have been extensively investigated. In particular, fear learning paradigms in rodents have been used as a model of PTSD pathogenesis.

In this regards, the modulatory role of ARBs in fear acquisition remains inconsistent. While previous work has shown that ARBs did not affect fear response to external threat (i.e. foot shocks) during fear acquisition (Marvar et al., 2014; Parrish et al., 2019), there is initial evidence suggesting ARBs reduced fear response to interoceptive threat (i.e. hypercapnia induced by C02 exposure) (Winter et al., 2019). In this study, it was shown in a contextual fear learning paradigm that ARB-treated animals not only exhibited a reduced fear response to interoceptive threat exposure, but also a reduced

fear response on the next day, when being re-exposed to the C02 associated chamber without C02 dispensation (Winter et al., 2019).

In contrast to fear acquisition, there is a wide body of animal research highlighting that ARBs improve fear extinction – the equivalent of human exposure-based therapy which is the gold standard for anxiety and PTSD treatment. It has been primarily shown that ARBs facilitate fear extinction consolidation rather than actual fear extinction training (Marvar et al., 2014; Parrish et al., 2019), but see (Quiñones et al., 2016). That is, ARB-treated animals did not differ from untreated animals in their fear response during the actual fear extinction training but show reduced fear response when being exposed to the threat cue on the next day. Similarly, it has been shown that ARBs facilitated fear memory reconsolidation resulting in reduced long-term fear responses (Swiercz et al., 2020). Yet, it remains to be confirmed whether ARBs improve fear extinction *generally* (Marvar et al., 2014), or if ARBs *specifically restore* dysfunctional fear extinction, for instance caused by experimental manipulation, such as lipopolysaccharide (LPS) injection (Quiñones et al., 2016), oestrogen downregulation (Parrish et al., 2019) or MAS-receptor deletion (Lazaroni et al., 2016), without affecting fear extinction which is not compromised (Parrish et al., 2019; Quiñones et al., 2016).

In humans, there is only one study on fear extinction (Zhou et al., 2019). In this study, 70 male healthy volunteers were administered a single dose of losartan or placebo after fear acquisition and prior to fear extinction. Results showed that ARB administration improved extinction learning, accompanied by increased vmPFC activity and increased amygdala and vmPFC coupling. Similarly, skin-conductance response during fear extinction was reduced in the losartan group.

Overall, previous research on the role of ARBs in fear conditioning show a similar pattern as research on the role of fear conditioning in PTSD. That is,

while the literature on the role of fear acquisition in PTSD pathogenesis remains inconclusive, PTSD-related aberrations in fear extinction have been consistently reported. Similarly, while the literature on the role of ARBs in fear acquisition remains inconsistent, it has been consistently shown that ARBs improve fear extinction.

1.5.3. The Effect of ARBs on Emotional Processing

There is a number of animal studies showing that ARB administration has direct anxiolytic effects (de los Angeles Marinzalda et al., 2014; Genaro et al., 2017; Llano López et al., 2012), for example when injected into the central amygdala (de los Angeles Marinzalda et al., 2014).

Consequently, human research has focused on elucidating the underlying mechanisms from a neurocognitive perspective using paradigms associated with amygdala functioning, emotional processing and reward learning. In this regard, it has been shown that a single dose of losartan facilitated amygdala activation to improve safety/threat discrimination of facial expressions (Reinecke et al., 2018). Similarly, it has been shown that ARBs modulate motivational behaviour to favour approach over avoidance tendencies, particularly in response to rewards. That is, losartan improved learning from positive relative to negative outcomes (Pulcu et al., 2019; Xu et al., 2023), and facilitated social reward processing relative to social punishment processing through midbrain-striatal-prefrontal circuit modulation (Zhou et al., 2023). This is in line with emotional memory research demonstrating that a single dose of losartan enhanced memory for positive relative to neutral material (Xu et al., 2022). Further, ARBs attenuated neural response to fearful stimuli in the oddball paradigm, reflected by reduced DLPFC activity for fearful stimuli and reduced amgygdala-dorsal ACC task-based functional connectivity (Zhang et al., 2023).

Taken together, ARBs demonstrate modulatory effects in various aspects of emotional processing, fear response and amygdala functioning. Their suggested role in promoting approach-oriented behaviour and reducing neural fear response, underscores their therapeutic potential for PTSD symptoms such as hypervigilance and avoidance behaviour.

1.5.4. The Effect of ARBs on Response Inhibition and Executive Control

Compared to the number of studies investigating emotional processing and amygdala function, the role of vmPFC-based response inhibition has only been brought into focus once. In this study, it was shown that losartan administration prior to fear extinction learning increased vmPFC activity and vmPFC-amydala coupling (Zhou et al., 2019). These results indicate that ARBs might counteract deficits in response inhibition, which have previously been observed in PTSD patients (e.g. DeGutis et al., 2015).

With regards to executive functioning more broadly, there is preliminary evidence suggesting that elderly patients taking ARBs as a hypertensive treatment performed better than patients on other hypertensive medication in behavioural markers of general executive function such as working memory (Ho et al., 2017; Yang et al., 2022) and task switching (Ho et al., 2017).

1.5.5. The Effect of ARBs on Memory and Hippocampal Processing

Despite the central role of aberrations in episodic memory formation and hippocampal functioning in PTSD psychopathology, only relatively little research has been conducted with ARBs in this context. In rodent models it was shown that ARBs restored memory function, for instance induced by MAS-receptor depletion (Lazaroni et al., 2012) or induced by chronic restrained stress (Wincewicz & Braszko, 2014a, 2014b; Wincewicz et al., 2016). Similarly, losartan administration improved long-term memory in a

model of Alzheimer disease through increased hippocampal neuroplasticity indicated by increased dendric spines (Coatl-Cuaya et al., 2022). Notably, ARB-induced enhancements in memory performance have also been replicated in elderly humans (Fogari et al., 2003; Fogari et al., 2006; Ho et al., 2017), but have gained relatively little attention outside the literature on Alzheimer disease and cognitive decline. More importantly, human neuroimaging work is sparse.

The only study investigating episodic memory functioning in a non-elderly sample used an emotional memory paradigm comparing the effects of a single dose of 50mg losartan vs placebo (Xu et al., 2022). It was shown that within the losartan group only, memory performance was enhanced for positive compared to neutral images, while memory performance between neutral and negative images did not differ (Xu et al., 2022). This behavioural effect was accompanied by reduced hippocampal activity during memory encoding for negative stimuli compared to neutral and positive stimuli within the losartan group. Meanwhile, in the placebo group hippocampal activity did not differ between encoding positive, neutral and negative images (Xu et al., 2022). However, since this study explores the intersection of emotional processing and memory formation, it remains unknown how ARBs affect general episodic memory formation.

Besides memory formation, ARBs may influence other hippocampal processes potentially relevant to PTSD. For instance, in animals studies it has been shown that ARBs enhanced hippocampal neuroplasticity markers, such as increasing dendric spines (Coatl-Cuaya et al., 2022), increasing brain-derived neurotrophic factor (BDNF) expression (Ping et al., 2014; Wincewicz et al., 2016) and promoting hippocampal neurogenesis (Drews et al., 2021; Ping et al., 2014). In fact, aberrations in hippocampal neurogenesis have been proposed to underlie vulnerability to psychiatric disease and PTSD (Anacker & Hen, 2017; Besnard & Sahay, 2016) and were linked to deficits in successful fear extinction (Yung-Wei et al., 2012).

In human studies, no research has explored ARB's effects on hippocampal functioning beyond emotional memory formation (Xu et al., 2022). As a behavioural proxy, however, it has been shown that losartan improved contextual processing of distressing film clips (Shkreli et al., 2020). Notably, although contextual processing has previously been associated with hippocampal functioning (Rudy et al., 2002; Smith & Bulkin, 2014), no neuroimaging was included in the above study.

1.5.6. The Effects of ARBs on the Stress Response

There is a broad body of research suggesting that ARBs play a regulatory role in the stress response, both the SNS and HPA-axis, with potentially important implications for stress-related disorders such as PTSD (for reviews, see Saavedra, 2012; Saavedra et al., 2005).

For instance, it has been shown in rodents that ARBs suppressed SNS activity, accompanied by lower urinary noradrenalin levels (Sueta et al., 2014). In the HPA-axis, it has been shown that chronically administered ARBs in rodents modulate CRF secretion, which is the hormone initiating the HPA-axis cascade. That is, CRF release in the paraventricular nucleus was decreased, when rodents were exposed to isolation stress after two-week candesartan administration (Armando et al., 2007).

Further, initial evidence suggests that HPA-axis modulation interacts with memory formation and anxiety response in rodents. In this study, rodents were exposed to 21 days of restraint stress while some animals also received ARBs during that period. As a result, corticosterone serum levels were decreased in the ARB treated rodents, while BDNF expression in the hippocampus was enhanced (Wincewicz et al., 2016). These endocrine effects were further accompanied by an improvement in stress-induced memory impairments and reduced anxiety-like behaviour (Wincewicz et al., 2016), highlighting an additional mechanism through which ARBs may modulate

neurocognitive processes relevant to PTSD – via shaping the stress response. However, these findings remain to be investigated and replicated in humans.

Notably, the lack of translational studies is reflective of a wider pattern, in which research into the central effects of ARB action has predominantly concentrated on animal models, with fewer studies directed towards understanding their implications in humans.

To initiate such translation in the SNS, there is initial evidence showing that a single dose of losartan reduced heart rate and heart rate variability during exposure to highly distressing film clips in healthy volunteers (Shkreli et al., 2020). Subsequently, visual processing of negative images and contextual processing of film-related images was facilitated in the losartan group compared to placebo (Shkreli et al., 2020). With regards to HPA-axis functioning, no study has investigated the role of ARBs in human research to the best of my knowledge, despite promising work in animal research.

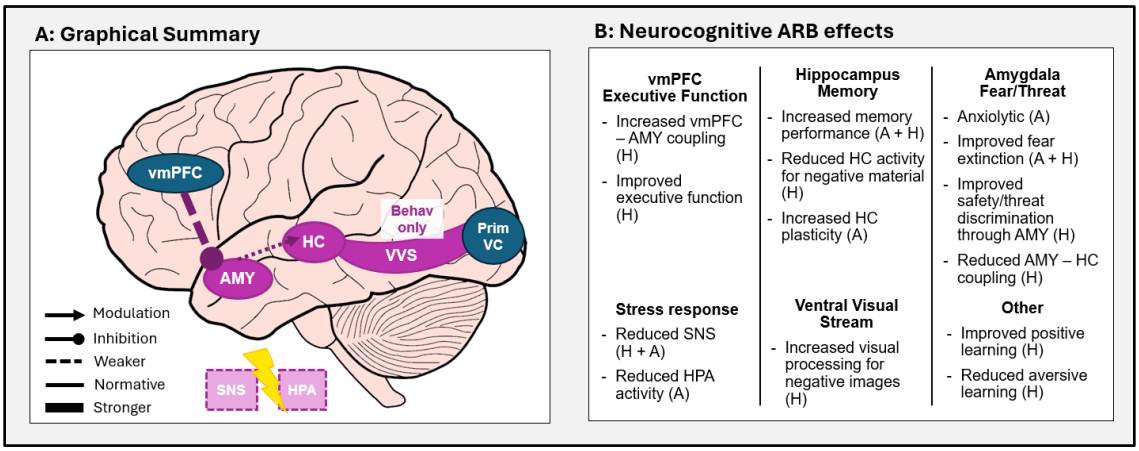


Figure 1.5. Summary of neurocognitive effects of ARB action. A: Purple colour represents the brain areas and connectivity between brain areas in which ARB effects have been demonstrated. Darker colour indicates an activity increase, whereas lighter colour indicates an activity decrease. The effect on the ventral visual stream (VVS), has only been shown in behavioural studies so far, hence the note on the illustration. The flash represents that ARB effects on the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis, where observed in response to stress exposure. **B:** Written summary of the key ARB effects in neurocognitive processing. 'A' indicates that results have been shown in animals. 'H' indicates that results have been shown in humans. vmPFC: ventromedial prefrontal cortex, AMY: amygdala, HC: hippocampus, prim VC: primary visual cortex.

1.6. ARBs and PTSD – Where Are We Now? Questions and Challenges

While there is accumulating evidence that ARBs may play an important modulatory role in PTSD psychopathology, the imperative next steps involve progressing fundamental research before their clinical application can be actualized.

First and foremost, most research on central ARB action has been carried out in rodent models. Thus, the application of these findings to the human population is limited, underscoring the need for translational studies to confirm the observed effects. While there have been population-based studies showing promising associations between regular ARB intake and reduced PTSD symptom development (Khoury et al., 2012; Seligowski et al., 2021), the neurocognitive mechanisms underlying these effects remain largely unexplored. However, a deep understanding of these mechanism is particularly important to inform the targeted use of ARBs and unfold their full clinical potential. Thus, conducting experimental studies in humansis crucial.

Second, it is required to extend experimental work not only from animals to humans, but also from emotional processing, fear learning and amygdala functioning to other neurocognitive domains relevant to PTSD pathogenesis. To date, most research has focused on investigating the role of emotional processing and amygdala function, given that ARBs have been primarily shown to reduce (i) anxiety-like behaviour in rodents (de los Angeles Marinzalda et al., 2014) and (ii) were associated with reduced PTSD symptom development in humans (Khoury et al., 2012; Seligowski et al., 2021). However, PTSD is a complex, multi-dimensional disorder characterized by abnormalities across various neurocognitive domains, while there is preliminary evidence that ARBs might modulate some of these processes. In particular, there is a wide body of ARB research in rodent models of Alzheimer's Disease and cognitive decline, showing that ARBs (i)

improve memory formation and hippocampal functioning in rodents (Coatl-Cuaya et al., 2022; Ongali et al., 2014), and (ii) memory performance in elderly humans (Fogari et al., 2003; Fogari et al., 2006). Given that PTSD development is closely linked to memory formation (Brewin, 2014; Ehlers & Clark, 2000) and characterised by functional and structural hippocampal aberrations (e.g. Joshi et al., 2020; Logue et al., 2018; Milad et al., 2009; O'Doherty et al., 2015), it is plausible to infer that hippocampus functioning in PTSD could also be modulated by ARB action. However, the link between the two domains of (i) fear/emotional processing models and (ii) memory-related Alzheimer disease models has not been fully recognised yet. This may be particularly important since recent evidence showed that the role of the amygdala in human fear learning seems to be less pronounced than initially suggested from animal models (Fullana et al., 2018; Fullana et al., 2016; Visser et al., 2021).

This leads to the third point: increased neuroimaging work is necessary. A thorough understanding of the neurocognitive mechanisms underlying ARB action requires direct investigation of brain activity, especially since the lack of human studies is parallelled by a lack of neuroimaging work. However, it is challenging to derive clear implications of central ARB action by solely investigating behavioural proxies, as behavioural processes are underpinned by neural activity of various brain structures. In particular, it is important to stress that brain structures do not operate in isolation, highlighting the importance of adopting a network perspective. In addition, it is important to take advantage of novel brain imaging analysis techniques. That is, neural processing is not only represented by the magnitude of brain activity, which is commonly investigated across studies, but also by its distinct neural activity patterns (Kriegeskorte et al., 2008). Consequently, comprehensive neuroimaging work using a variety of methodologies is essential to advance our understanding of the role of ARBs in PTSD psychopathology.

Lastly, the role of ARB modulation in stress and the HPA-axis needs to be examined in humans, given the crucial role of stress in PTSD psychopathology and PTSD-related neurocognitive processes. Initially, it is essential to establish whether ARBs modulate HPA-axis functioning as suggested by animal models (Armando et al., 2007; Wincewicz et al., 2016), and replicate initial associations in humans showing reduced SNS activity in response to acute ARB administration (Shkreli et al., 2020). Subsequently, in terms of positive results, it remains to be directly investigated whether ARBs modulate neurocognitive processing through their proposed involvement in the stress response.

Ultimately, once the fundamental work into ARB action has progressed, it is equally important to take the next step and probe these finding in clinical settings, for instance by using randomized-controlled-trials, to advance potential clinical applications for PTSD in the future.

1.7. Aim of this Thesis

Given the early stages of ARB research on human cognition and psychopathology, this thesis aims to examine the role of ARBs on PTSD-related neurocognitive domains which remained relatively under-explored, despite their potential crucial role in the disorder's pathogenesis. Using the most widely studied ARB losartan in a series of double-blind placebo-controlled experiments, this thesis expands previous work on the neurocognitive underpinnings of ARB action by focusing on memory formation, functional brain connectivity and stress - with a particular emphasis on employing multimethodological neuroimaging analysis techniques.

Chapter 2 investigates the effects of losartan on memory encoding in high-anxious volunteers, employing univariate fMRI analyses on a memory paradigm consisting of images of animals and landscapes. This chapter seeks

to uncover the specific brain areas in which losartan exerts its effects during memory encoding via comprehensive whole-brain analyses and a targeted hippocampus region-of-interest analysis, as the core brain area for memory formation.

Building on the foundational work of that data chapter, Chapter 3 employs a more advanced methodology of multivariate pattern similarity analysis to unravel nuanced effects of losartan on memory formation in the same high-anxious volunteer sample. In contrast to mean activity differences investigated via univariate analyses, this approach allows to examine changes in fine-grained neural activity *patterns* during memory encoding, offering a more detailed understanding of how ARBs influence neural memory formation.

Complementing task-based changes in neural processing, chapter 4 examines the effect of losartan on the brain's intrinsic organization via resting state functional connectivity in high-anxious volunteers. Using data-driven independent component analysis and hypothesis-driven seed-based analyses, this chapter aims to investigate the potential modulatory role of ARBs on the connectivity of intrinsic neural networks which underpin cognitive and emotional processing.

Moving beyond neural effects of ARBs, chapter 5 explores the role of losartan in modulating the endocrine and physiological stress response in healthy volunteers. Focusing on HPA axis activity (cortisol secretion), physiological stress (heart rate) and SNS activity (heart rate variability) this chapter aims to provide a comprehensive overview of how losartan modulates key factors in the stress response pathway, which is an important mechanism underlying fear and stress-related disorders. Additionally, this chapter seeks to unravel potential interaction effects between losartan, stress response and hormonal contraception, considering the significant role of sex hormones in cortisol

secretion and preliminary evidence of sex hormone modulation in ARB action.

2

Chapter 2
ARB Effects on Memory Formation

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Key abbreviations

ACC: Anterior Cingulate Cortex

BOLD (signal): Blood-Oxygen-Level-Dependent

fMRI: Functional Magnetic Resonance Imaging

PHC: Parahippocampal Gyrus

ARBs Effects on Memory Formation

The investigation into neurocognitive ARB effects in this thesis starts with memory formation. This chapter aims to elucidate how ARBs influence memory encoding processes using fMRI, given the critical role of memory aberrations and hippocampal functioning in PTSD development. To initiate clinical applicability, a sample of high-trait anxious volunteers has been recruited.

Note. The majority of this chapter was published in:

Shkreli, L., Thoroddsen, T., Kobelt, M., Martens, M. A., Browning, M., Harmer, C. J., ... & Reinecke, A. (2024). Acute Angiotensin II Receptor Blockade Facilitates Parahippocampal Processing During Memory Encoding in High-Trait-Anxious Individuals. *Biological Psychiatry Global Open Science*, 4(2), 100286.

2.1. Introduction

In the past decade, research has increasingly implicated a key role of the renin-angiotensin-system (RAS) in the development of anxiety and post-traumatic stress disorder (PTSD). Although this endocrine system is mainly involved in vascular contraction and blood pressure regulation (Peach, 1977), angiotensin-II receptors are expressed in brain areas relevant for cognition and psychopathology, such as amygdala and hippocampus (von Bohlen und Halbach & Albrecht, 2006). In rodents, increased angiotensin-II levels are seen in response to stress, which plays a pivotal role in anxiety development (Braszko et al., 2003; Duchemin et al., 2013). Importantly, drugs targeting RAS activity – most notably angiotensin-II receptor blockers (ARBs) such as losartan – were associated with reduced PTSD symptom development in population-based studies (Khoury et al., 2012; Seligowski et al., 2021),

highlighting how studying the RAS in fear-related disorders may inform new curative and preventative developments.

Mechanistically, ARBs seem to target fundamental neurobiological processes in anxiety and PTSD. For instance, single-dose losartan blunted the sympathetic stress response to highly distressing film material in a human PTSD model (Shkreli et al., 2020), while ARB administration in rodents directly reduced anxiety-like behaviour (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012). Similarly, ARBs improved fear extinction (Khoury et al., 2012; Zhou et al., 2019), 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 the involuntary recall of traumatic events, known as memory intrusions. Notably, reduced grey matter volumes in PTSD have been consistently reported in the core brain area for episodic memory formation – the hippocampus (Pitman et al., 2012) – but also other cortical structures in the extended memory network such as the parahippocampal gyrus (PHC) (Crombie et al., 2021). Thus, memory formation needs to be specifically addressed in human work, especially since the hippocampus is modulated by ARB action (Jackson et al., 2018). For instance, ARBs induced hippocampal neurogenesis in rodents (Drews et al., 2021; Ping et al., 2014), while reduced hippocampal neurogenesis has been associated with dysfunctional contextualization of memory traces (Denny et al., 2014), which is believed to contribute to memory intrusions in PTSD (Brewin et al., 2010).

Furthermore, preliminary evidence indicates that ARBs might counteract episodic memory aberrations often seen in PTSD (Brewin et al., 2007; Samuelson, 2011), as ARBs increased memory performance and prevented cognitive decline in elderly humans (Fogari et al., 2003; Fogari et al., 2006).

Similar effects were present in rodents (Bild et al., 2013; Drews et al., 2021; Salmani et al., 2020), where ARBs further enhanced hippocampal long-term potentiation (Hosseini et al., 2021), the core cellular mechanism in learning and memory (Bliss & Collingridge, 1993). Notably, PTSD patients perform more poorly than healthy controls and trauma-exposed individuals in episodic memory tasks (Brewin et al., 2007) affecting neutral (Carrión et al., 2010; Guez et al., 2011; Samuelson, 2011) and emotional material (Noriega et al., 2021), as well as autobiographical events (Schönfeld & Ehlers, 2017). In turn, improvements in episodic memory performance were associated with PTSD symptom improvement post-treatment in a longitudinal study (Dickie et al., 2011), while symptom reduction was predicted by higher activity in the hippocampus and anterior cingulate cortex (ACC) during pre-treatment memory encoding (Dickie et al., 2011). 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 on the memory system.

Given that (i) population-based studies associate ARBs with reduced PTSD symptom development (Khoury et al., 2012; Seligowski et al., 2021), (ii) PTSD is characterized by episodic memory aberrations (Brewin et al., 2007; Samuelson, 2011), and (iii) ARBs enhance memory function (Bild et al., 2013; Drews et al., 2021; Fogari et al., 2003; Fogari et al., 2006; Salmani et al., 2020), we investigated the effect of acute ARB administration on memory formation in high-trait anxious volunteers to initiate PTSD applicability. In a double-blind randomized design, we investigated episodic memory encoding during fMRI using images of animals and landscapes. This paradigm has been shown to sensitively capture memory formation and hippocampal functioning (de Cates et al., 2021; Filippini et al., 2009).

Based on the rapid cognitive effects of losartan (Pulcu et al., 2019; Reinecke et al., 2018; Shkreli et al., 2020) we hypothesized that one dose improves

memory performance and enhances hippocampal processing during memory encoding.

2.2. Methods and Materials

2.2.1 Participants

We recruited 41 high-anxious participants (34 women) with a STAI-T score >40 (Spielberger Trait Anxiety Inventory; Spielberger et al., 1970).

Sample size calculations were based on the effect of a single dose of losartan on a behavioural marker of prospective memory in healthy volunteers (Mechaeil et al., 2011), the only available study on ARB memory effects at the time of protocol design (50 mg losartan, M=5.9, SD=1.6; placebo M=3.9, SD=2.0, d=1.05, see Mechaeil et al., 2011). G-Power suggested a sample size of 18 per group to achieve power of at least 0.85 at an α-level of 0.05 in a two-sided independent-samples t-test. The target sample size was inflated to account for an anticipated 10% data loss due to poor scan quality or movement.

Participants were recruited from the public through posts on noticeboards, social media and mailing lists. They were included if they were aged 18-50, had a body mass index of 18-30, not pregnant/breastfeeding, smoking <5 cigarettes/day, not taking any central-nervous-system active medication in the past 6 weeks, not taking any blood pressure medication or aliskiren, not suffering from serious medical conditions, no personal or family history of a severe psychiatric condition, no contraindication to MRI. Apart from demographics, the following questionnaires were included to describe the sample: Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975), Anxiety Sensitivity Inventory (Taylor & Cox, 1998), Beck Depression Inventory-II (Beck et al., 1996), Attention Control Scale (Derryberry & Reed,

2002), Behavioural Inhibition and Activation Scale (Carver & White, 1994). All participants gave written informed consent.

2.2.2. Procedure

The study received ethics approval from the University of Oxford Medical Sciences Research Ethics Committee (ethics reference: R58494/RE004). During an online screening, participants were interviewed about their medical history, followed by a psychiatric screening using the structured clinical interview for DSM-5 (SCID-V First et al., 2016), and the spot the word test (STW; Yuspeh & Vanderploeg, 2000) to estimate verbal intelligence. Eligible participants were invited to a face-to-face session, and randomly allocated to receive either a single dose of 50mg losartan (Cozaar; Merck Sharp & Dohme Ltd) or matched placebo (microcrystalline cellulose; Rayotabs, Rayonex GmbH), stratified for sex by an independent researcher to preserve double-blindness. The randomisation used a blocked method (blocks of four) with the sequence generated by a random number generator (www.random.org).

Losartan and placebo pills were over-encapsulated by an independent researcher to look identical, prior to being placed in an envelope labelled with the participant ID. These envelopes were handed to the experimenter the day before the testing session. The dose of 50mg was chosen based on previous research (e.g. Pulcu et al., 2019; Reinecke et al., 2018; Shkreli et al., 2020), which showed that it is well tolerated, modulates neurocognitive processing, and has no significant physiological effects on heart rate or blood pressure.

On the face-to-face testing day, blood pressure and heart rate were measured before drug administration and at drug peak level (1hr after intake; Lo et al., 1995; Ohtawa et al., 1993), together with visual analogue scales (VAS) assessing physiological symptoms and mood state to ensure that there were no

potential confounding effects on cognitive outcomes. Subsequently, participants completed the memory paradigm consisting of a pre-scan encoding phase, pre-scan recognition test, main encoding phase during fMRI, and the main recognition test 1hr after fMRI. Subsequently, participants and experimenter guessed group allocation.

2.2.3. Memory Paradigm

During pre-scan encoding, participants viewed the same 8 images (4 animals, 4 landscapes) 8 times in pseudorandom order (2s per image, interstimulus interval 500ms), 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' block, each block contained all 8 familiar images) and 6 blocks of 8 not previously seen images each time ('novel' block, each block contained 8 different images). Novel and familiar blocks were presented in alternating order with a 12s fixation cross between them as baseline. Within blocks, images were presented pseudorandomly for 2s (interstimulus interval 500ms) to be identified as animals or landscapes and memorized.

In the main recognition test, 1hr after fMRI, participants were presented all images seen during fMRI (8 familiar, 48 novel) and 27 additional new images to be recognized as 'old' (i.e. seen during fMRI) or 'new' (figure 2.1.).

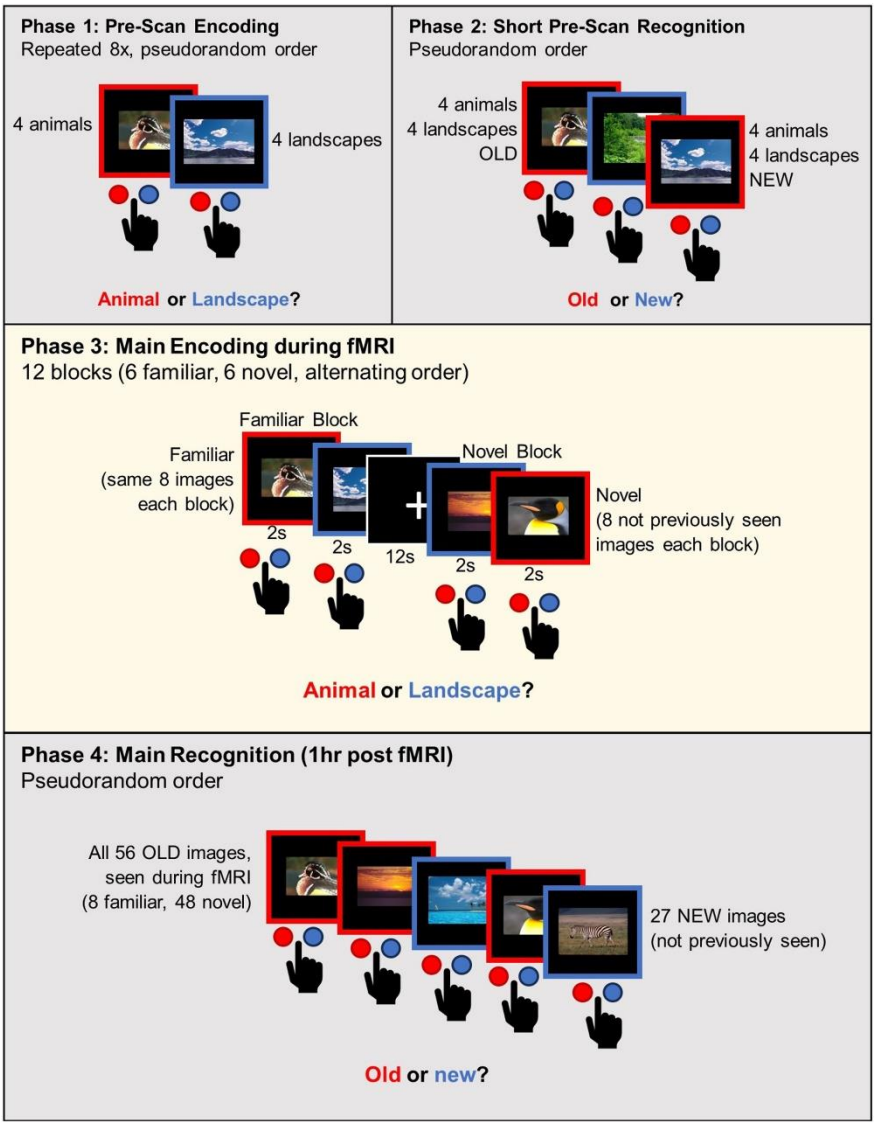


Figure 2.1. Overview of the Memory Task. In the pre-scan encoding phase (phase 1), participants are instructed to repeatedly identify the same 8 pictures as animals or landscapes. In pre-scan recognition phase (phase 2), participants are presented the 8 pictures from pre-scan encoding and 8 new pictures 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 fMRI (phase 3), participants are presented with alternating blocks of the same 8 familiar images, and blocks of each time not previously seen images (from here referred to as 'novel images'). They are instructed to identify the images as animals or landscapes and memorize them. During the main recognition test (phase 4), participants indicated whether the images are old (i.e. 8 familiar images and 48 novel images, seen during fMRI) or new (27 images, not previously seen during any experimental phase). Note than only the main encoding phase (phase 3) is conducted during the fMRI scan.

2.2.4. MRI Data Acquisition

MRI data was acquired at the Oxford Centre for Human Brain Activity using a 3T Siemens MAGNETOM Prisma scanner (Siemens, Erlangen, Germany) with a 32-channel head-coil.

High-resolution T1-weighted images were acquired using a MPRAGE sequence with the following parameters: resolution=1mm x 1mm x 1mm, TR=1900ms, TE=3.97ms, TI=904ms, flip angle=8°, field of view acquisition matrix=174x192x192, acquisition time: 5min 31s). Blood-oxygenation-level-dependent (BOLD) functional MRI data was acquired in a single run using an EPI multiband sequence (factor 6) with the following parameters: resolution=2.4mm x 2.4mm x 2.4mm, TR=800ms, TE=30ms, flip angle=52°, field of view acquisition matrix = 216x216x144, acquisition time: 6min 48s. A respective single-band reference images was used to improve multiband registration during pre-processing. For distortion correction field maps were acquired using 2D gradient echo (resolution=2.4mm x 2.4mm x 2.4mm, TR=590ms, TE1=4.92ms, TE2=7.38, field of view acquisition matrix=216x216x144, acquisition time: 1min 47s).

2.2.5. MRI Data Preprocessing

MRI preprocessing and analysis was conducted using FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). All MRI data was converted to standardized BIDS-format (Brain Imaging Data Structure) using heudiconv (https://github.com/nipy/heudiconv) prior to being pre-processed and analysed.

Structural T1-weighted images were brain extracted using the FSL brain extraction tool 'BET' (Smith, 2002). Preprocessing of functional images included BET brain extraction, motion correction using MCFLIRT (Jenkinson et al., 2002), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering with

a cut-off value of 90s (Gaussian-weighted least-squares straight-line fitting, with sigma = 45s), B0-unwarping using fieldmap rads and magnitude images, prewhitening using FILM, and correction for differences in slice acquisition time using temporal derivatives.

For univariate BOLD analyses spatial smoothing was applied using a Gaussian kernel of 5mm full width at half maximum (FWHM). Further, EPI functional images were registered to their T1-weighted structural space with FLIRT (FMRIB's Linear Image Registration Tool), using a single band reference image and the BBR method (Boundary-Based Registration). The subsequent non-linear registration to MNI standard space was conducted using FNIRT (FMRIB's Non-Linear Image Registration Tool) and a resampling resolution=2mm.

To control for potential volumetric difference, grey matter maps were created using FSL GMprepare to be used as a control regressor in subsequent analyses

2.2.6. MRI Data 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, one regressor for familiar images and one for novel images were modelled including their temporal derivatives to account for small timing deviations in the HRF peak and improve the overall fit of the model. . 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 grey matter maps to correct for potential volumetric differences. Whole-brain mixed-effect analysis with FLAME 1+2 and a cluster-based thresholding of $z>3.1$, familywise error corrected (FWE) $p<0.05$ 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 (PEs) from the hippocampus ROI to conduct a 2x2 mixed-model ANOVA with the between factor drug group (losartan, placebo) and within-factor image condition (novel, familiar).

2.2.7. Behavioural Analysis

All analyses were performed using SPSS software version 29 (IBM SPSS, Inc., Armonk NY) with an alpha-level of α=0.05. To test that drug administration did not change any physiological parameters or VAS ratings, we conducted 2x2 mixed model ANOVAs with the between factor group (losartan, placebo) and the within factor time (pre administration, peak administration), in which a statistically non-significant group x time interaction effect reflects no drug-induced changes. To test for behavioural group differences in identification accuracy during encoding (i.e. sum of correctly identified images as animals/landscapes) and memory recognition, we used independent samples two-tailed t-tests. Memory recognition was reflected by the discrimination index 'P_r' (Pr = hit rate - false alarm rate; Snodgrass & Corwin, 1988), 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) x condition (novel, familiar) mixed-model ANOVA on reaction times to test whether losartan administration modulated the time to identify images as animals or landscapes.

2.3. Results

2.3.1 Participant Characteristics and Acute Drug Effects

The groups were comparable across all sociodemographic, clinical, attentional and personality trait questionnaire measures (table 2.1.). There

were no acute drug effects on blood pressure and heart rate (all *p*s>.31, table 2.2.), nor on changes in mood and physiological VAS ratings from baseline to drug-peak level (all *p*s>.08, table 2.2.), 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-blindness was maintained.

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

Table 2.1. Participant Characteristics. Overview of sociodemographic measures as well as attentional, clinical and personality participant characteristics in the placebo and losartan group

	Placebo (N=20; 17 female)	Losartan (N=20; 16 female)
	M (SD)	M (SD)
Sociodemographic Measures		
Age	27.15 (9.26)	27.17 (9.63)
Verbal Intelligence	100.14 (20.59)	107.53 (10.89)
Years of Education	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)

Note: ACS: Attentional Control Scale, BDI: Beck Depression Inventory, BIS: Behavioral Inhibition Scale, BAS: Behavioral Activation Scale, ASI: Anxiety Sensitivity Index, STAI-T: Spielberger's Trait Anxiety Inventory, EPQ = Eysenck Personality Inventory

Table 2.2. Group comparisons in physiological parameters and visual analogue scale (VAS) ratings taken before drug intake and at drug peak-level.

	Baseline		*Drug Peak Level*		
	Placebo	Losartan	Placebo	Losartan	
	M (SD)	M (SD)	M (SD)	M (SD)	p
Physiological Measures					
Heart Rate	78 (11)	78 (17)	69 (7)	70 (11)	.84
Systolic BP	113 (12)	120 (15)	111 (11)	113 (14)	.31
Diastolic BP	69 (8)	73 (11)	68 (8)	71 (11)	.96
VAS Ratings					
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)	.60 (1.23)	.25 (.98)	.93
Tearful	.45 (.95)	.65 (.93)	.15 (.37)	.25 (.55)	.74
Nauseous	.85 (1.76)	.25 (.55)	.70 (1.46)	.45 (.76)	.09
Hopeless	.75 (1.59)	.55 (.89)	.60 (1.24)	.25 (.55)	.50
Tremor	.30 (.57)	.40 (.68)	.25 (.55)	.30 (.57)	.77
Sad	1.25 (1.65)	1.05 (1.00)	.95 (1.57)	.40 (.68)	.29
Dizzy	.20 (.41)	.25 (.71)	.60 (1.10)	.55 (.95)	.71
Depressed	1.25 (1.74)	.70 (.98)	.80 (1.47)	.50 (.69)	.28
Heart Racing	.95 (1.28)	.70 (1.03)	.30 (.73)	.85 (1.05)	.08
Alert	5.05 (2.44)	5.65 (2.82)	4.40 (2.80)	4.35 (2.70)	.54

Note: BP: Blood Pressure; Heart rate is presented in bpm. Systolic and diastolic blood pressure are presented in in mmHg. p-values refer to the statistical level of significance of group x time interaction effect.

2.3.2. Behavioural Task Analysis

Image Identification at Encoding. Both groups performed equally well in identifying images as animals or landscapes (% correct losartan: M=96.30, SD=11.49; placebo: M=95.31, SD=11.34; $t(38)$=-.27, p=.79, d=-.09). The group (losartan, placebo) x condition (novel, familiar) ANOVA on response time revealed that both groups were faster in correctly identifying familiar images as animals/landscapes than correctly identifying novel images as animals/landscapes (familiar M=.72, SD=.13; novel M=.82, SD=.17; main effect

condition $F(1,38)= 79.32$, $p<.001$, $\eta_p^2=-68$). This is expected, as familiar images have been repeatedly presented, therefore requiring less visual discrimination. While there was no main effect of group on response time ($F(1,38)=2.69$, $p=.11$, $\eta_p^2=.07$), there was a trend for a group x condition interaction effect ($F(1,38)=3.55$, $p=.07$, $\eta_p^2=.09$) towards the losartan group being faster at identifying novel images as animals/landscapes (losartan $M=.77$, $SD=.15$; placebo $M=.86$, $SD=.18$, $t(38)=1.81$, $p=.08$, $d=.57$) but not familiar images (losartan $M=.70$, $SD=.12$; placebo $M=.75$, $SD=.13$, $t(38)=1.36$, $p=.18$, $d=.43$), potentially reflecting a drug-induced visual processing advantage for not previously seen images (figure 2.2.).

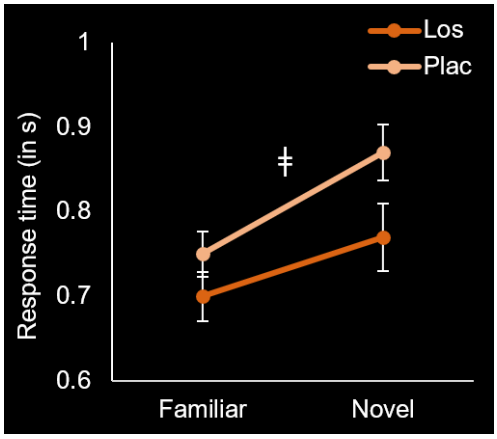


Figure 2.2. Visualization of Response Time to identify images as animals/landscapes in the main encoding phase during fMRI. Both groups were faster in identifying familiar images compared to novel images. Familiar images have been previously seen during the pre-scan memory encoding phase, while novel images consisted of not previously seen images. The losartan group is faster in identifying novel images compared to the placebo group at trend level. Los: Losartan; Plac: Placebo; ǂ: p = .07.

Memory Recognition. Independent samples t-test on the P_r score showed no group differences in recognition performance (losartan: $M=.53$, $SD=.14$; placebo: $M=.54$, $SD=.17$; $t(38)=.20$, $p=.85$, $d=.06$).

2.3.3. Memory paradigm fMRI

Basic task effects. Task effects on neural memory encoding were determined by comparing BOLD signal for novel vs familiar images across groups, as novel images require memory formation in contrast to familiar images which have already been encoded pre-fMRI. Consistent with previous findings (de Cates et al., 2021; Filippini et al., 2009), the task activated the memory network consisting of visual occipital areas, temporal fusiform cortex, parahippocampal gyrus (PHC), and hippocampus (figure 2.3.-A).

Losartan effects on univariate BOLD signal – Whole brain analysis. Losartan administration changed neural response to novel and familiar images. In the whole-brain analysis for familiar images (vs baseline), three clusters were identified in which BOLD signal was greater for the losartan group compared to placebo, including the PHC, ACC and caudate (for detailed cluster information, see figure 2.3-B,C.). For novel images (vs baseline), one cluster in the PHC showed greater BOLD signal in the losartan group compared to placebo (for detailed cluster information, see figure 2.3-B,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 vs familiar contrasts (i.e. novel>familiar, novel<familiar).

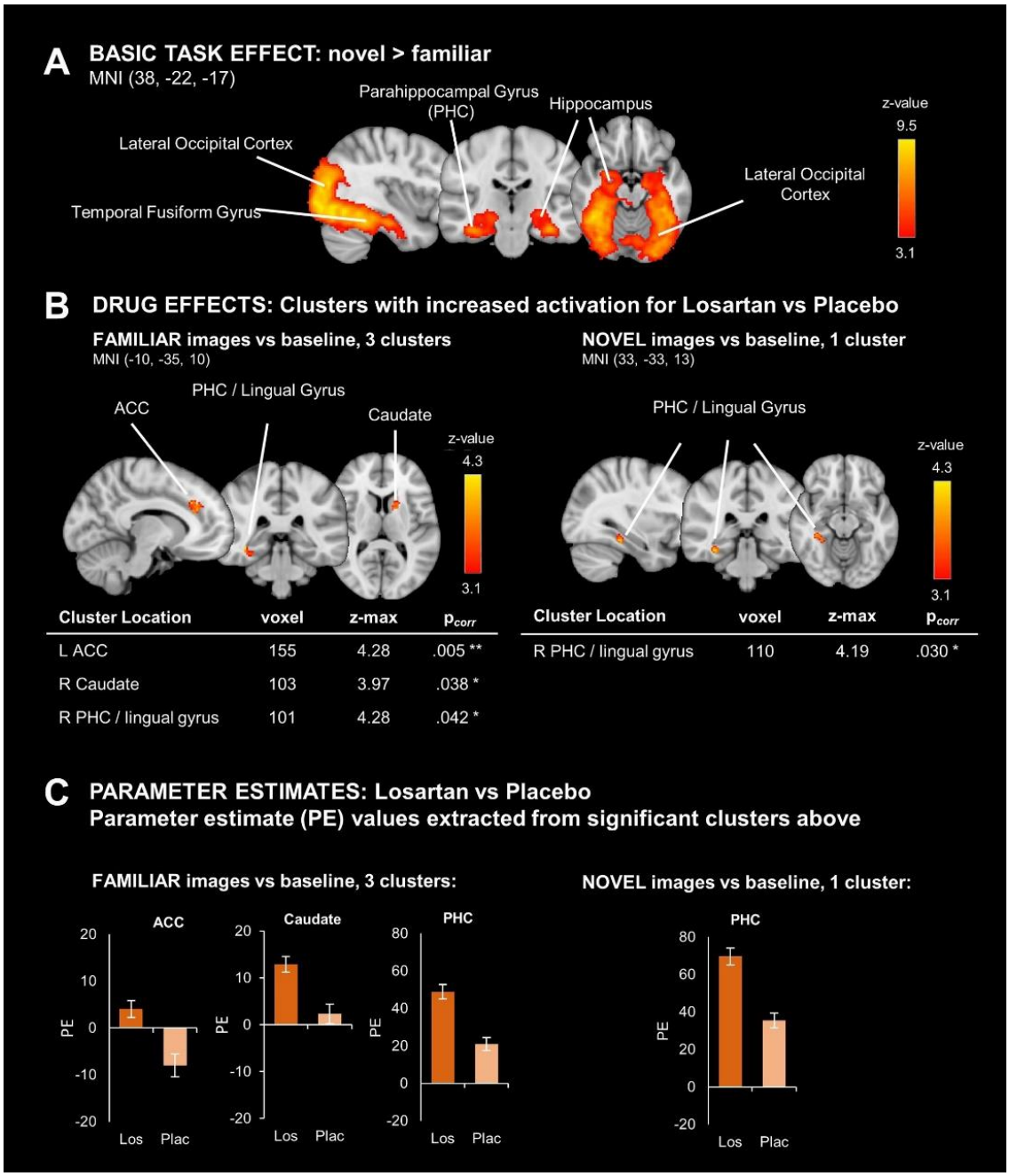


Figure 2.3. Univariate fMRI analyses. A: Basic task effects (novel > familiar, across all 40 participants; $z > 3.1$, $p < 0.05$ family-wise-error (FWE) corrected); depicted is the largest cluster from this analysis, which consists of regions from the memory network. **B:** Depicted are the significant clusters in which the losartan group showed increased activation compared to the placebo group, for familiar images vs baseline (left) and for novel images vs baseline (right). Statistics are based on $z > 3.1$, $p < 0.05$ FWE corrected. The tables below contain additional information of the significant clusters, i.e. cluster location, cluster size in voxel, max z-value, FWE-corrected p-value. *$p < 0.05$ corrected; **$p < 0.01$ 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 compared to the placebo group. Error bars represent the standard error. Los = losartan; Plac = placebo.

Losartan effects on univariate BOLD signal – Region-of-interest analysis. In the hippocampus ROI, the group (losartan, placebo) x condition (familiar, novel) ANOVA showed greater BOLD signal in response to novel compared to familiar images across groups (novel: M=6.50, SD=9.55; familiar: M=.69, SD=8.58; $F(1,38)=27.87$, $p<.001$, $\eta_p^2=.42$), confirming greater hippocampal activation during memory encoding of not previously seen images. However, there was no main effect of group ($F(1,38)=.35$, $p=.56$, $\eta_p^2=.01$), nor a group x condition interaction effect ($F(1,38)=.38$, $p=.54$, $\eta_p^2=.01$), suggesting that losartan did not modulate hippocampal BOLD response.

To explore whether losartan differentially affects BOLD response over the course of the task, such as having early effects diminishing over time, we conducted an exploratory group (losartan, placebo) x block (1-6) ANOVA for novel and familiar images. However, there were no group main effects, nor group x block interaction effects (all ps> .33; figure 2.4.).

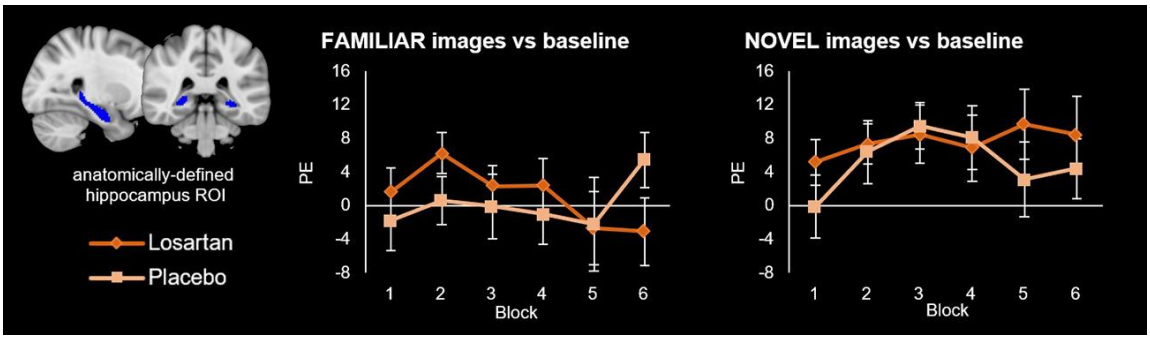


Figure 2.4. Hippocampus Region-of-interest (ROI) analysis. Groups do not differ in their BOLD signal over the course of the task. The Parameter Estimates (PEs) per block are extracted from an anatomical hippocampus mask (Harvard-Oxford cortical structural atlas)

2.4. Discussion

This study investigated the neural effects of ARBs on memory encoding processes 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. Contrary to our expectations, the drug had no effect on hippocampal BOLD response nor behavioural memory recognition. However, there was a trend of losartan facilitating 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 (Eichenbaum et al., 1996). These areas are substantial for memory formation, as they modulate the sensory information forwarded to the hippocampus (Squire et al., 2015). The PHC is involved in processing associations between spatial, scene and context information during memory formation (Aminoff et al., 2013; Eichenbaum & Lipton, 2008) and is considered a higher-order visual processing area at the end of the ventral visual stream particularly responding to naturalistic scenes (Dwivedi et al., 2021; Epstein et al., 2003; Mohsenzadeh et al., 2020). In turn, aberrations in these primarily higher-order visual processes have been associated with PTSD symptom development and memory intrusions (Meyer et al., 2017), which are believed to be provoked by fragmented memory encoding (Ehlers & Clark, 2000).

This study proposes a new mechanism in 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 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* induced by losartan would have required a differential BOLD response to novel vs familiar images which is absent in our study, aligning with a lack of losartan effects on the hippocampus or behavioural memory performance.

Conversely, behavioural 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 memory encoding advantage, although this was not statistically significant. Thus, we propose that rather than directly enhancing memory formation, ARBs might 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 not previously seen negative images (Shkreli et al., 2020).

Furthermore, an ARB enhancement of visual processing and PHC activity may modulate memory intrusions, which are believed to be triggered by perceptually similar cues through elevated priming (Ehlers & Clark, 2000; Ehlers et al., 2006). In turn, elevated priming was underpinned by decreased PHC activity (Yang et al., 2008). In particular, during visual repetition priming, in which the same visual stimuli are repeatedly presented, it was shown that PHC activity decreased along repetitions as a marker of neural priming response (Raposo et al., 2006; Soldan et al., 2010). This is comparable to the repeated presentation of familiar images in our paradigm, for which ARBs increased PHC activity, which suggests that the neural priming response was less pronounced. Hence, our results may imply a potential mechanism through which ARBs could further be involved in alleviating the development of memory intrusions following trauma. However, targeted research is needed to investigate our proposed trajectory by which changes in visual processing contribute to PTSD manifestation and treatment.

In contrast to neural effects on the memory network, the lack of behavioural 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 behavioural level, unlike previous research using chronically prescribed ARBs for hypertensive treatment (Khoury et al., 2012; Seligowski et al., 2021), including studies reporting positive memory effects in the elderly (Fogari et al., 2003; Fogari et al., 2006). Hence, more chronic use of ARBs or samples with higher variability in memory performance may reveal clear behavioural memory effects.

Similarly, no group differences in memory performance between a single-dose losartan and placebo were observed in an emotional memory paradigm in a non-elderly sample (Xu et al., 2022). Instead, recognition was reduced for negative relative to neutral images within the losartan group only. This suggests ARBs improve emotional modulation during memory formation rather than memory performance, and it is in line with previous work showing that losartan reduced learning from negative feedback in a reinforcement paradigm (Pulcu et al., 2019). 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 (Jhang et al., 2018), while preliminary evidence highlights caudate involvement in altered reward-based decision making in PTSD (Boukezzi et al., 2020). Together, it seems plausible that ARBs at least partially influence emotional processing or emotion-memory interactions, rather than universal memory formation. Alternatively, although the ACC is a structure within the limbic system which has primarily been implication in emotional response and fear learning (Etkin et al., 2011), there is evidence showing its involvement in attentional control and sustained attention (Newman & McGaughy, 2011; Segalowitz & Dywan, 2009). Thus, it may also be plausible that increased ACC activity for familiar images reflect increased sustained attention, complementing the interpretation of increased visual processing through PHC activation. Taken together, this interpretation would indicate that despite the repeated presentation of familiar images, ARBs maintain

higher cognitive engagement with the presented stimuli through modulating attention (ACC) and visual processing (PHC).

Previous work in humans has centred on examining ARB effects on fear learning and amygdala response, based on encouraging rodent work showing anxiolytic (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012), stress-reducing (Pavel et al., 2008) and fear-extinction enhancing effects (Marvar et al., 2014). However, direct human translation remains difficult even in well-established neurocircuits. For instance, the role of the amygdala in fear conditioning is less clear in human fear responses compared to rodents (Fullana et al., 2018; Fullana et al., 2016; Visser et al., 2021), while rodent models cannot fully capture the cognitive components underlying psychiatric disease (Flores et al., 2018). On the other hand, rodent work is essential for a fine-graded understanding of ARB action, such as elucidating the importance of AT1 and AT2 receptor interplay (Yu et al., 2019) 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 (Braszko et al., 2006; Royea et al., 2017; Wright & Harding, 2013). Angiotensin-IV has been shown to improve memory formation (Gard, 2008; von Bohlen und Halbach, 2003), although the precise receptor-mediated pathways remain to be established (Chow et al., 2015; Gard, 2008; Wright & Harding, 2011). Taken together, 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, the block design of the memory paradigm limits our ability to investigate refined neural mechanisms during memory encoding, which may potentially explain the lack of losartan effects. For example, familiar blocks consisted of the same images each time, whereas novel blocks contained entirely new images each time. Thus, we cannot rule out that the novel vs. familiar contrast, employed

to investigate memory encoding, may be confounded by differences in visual processing of non-repeatedly presented vs repeatedly presented images. In addition, novel blocks included images that were later remembered and those that were later forgotten, so that the mix of remembered and forgotten items may have further confounded the novel vs familiar contrast. To address both these issues, an event-related design with no repeated image presentations would be more appropriate. This approach would not only allow remembered and forgotten trials to be modelled as separate regressors in the GLM, but also eliminate the confound of visual processing since no images would be presented multiple times. Moreover, future studies could use an fMRI sequence optimized for the hippocampus to further enhance sensitivity in detecting any potential effects of losartan on this region.

In addition to the limitations of the block design, we cannot establish whether losartan acts directly or indirectly on the PHC, given it remains unclear whether AT1 receptors are expressed in the PHC, or only in adjacent areas (von Bohlen und Halbach & Albrecht, 1998; von Bohlen und Halbach & Albrecht, 2006). Our sample being predominantly female may restrict generalizability to the general population, yet it holds increased clinical relevance due to women being more than twice as affected by anxiety disorders and PTSD than men (Kilpatrick et al., 2013; McLean et al., 2011). Additionally, sex differences are seen in RAS activity and in response to ARBs due to their role in oestradiol modulation (Hajmohammadi et al., 2019; Miller et al., 2006; O'Hagan et al., 2012; Parrish et al., 2019). Thus, future studies may wish to ensure adequate statistical power to assess gender effects and preregister their design and analyses, which was not performed here. Further, 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, where clinical studies are needed to establish the proposed effects in PTSD.

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 take a step towards PTSD applicability. We further extend previous work by highlighting that ARBs might 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 might lead to the suggested preventative effects of ARBs in PTSD development. Our results therefore highlight the importance of exploring the role of the RAS on higher-order sensory deficits in future research.

3

Chapter 3
Unravelling ARB Memory Effects using Pattern Similarity

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Key abbreviations

MVPA: Multivoxel Pattern Analysis

PHC: Parahippocampal Gyrus

PS: Pattern Similarity

PSA: Pattern Similarity Analysis

Unravelling ARB Memory Effects using Pattern Similarity

This chapter builds on the previous chapter on investigating ARB effects in memory encoding by introducing a refined methodological approach through multivariate pattern similarity analysis. Instead of investigating mean activity, pattern similarity analysis investigates voxel activity patterns to advance a more refined comprehension of central ARB action. While such multivariate approaches have widely been used in basic neurocognitive research, they have only recently begun to be translated into more clinically relevant questions.

Note. Parts of this chapter were published in:

Shkreli, L., Thoroddsen, T., Kobelt, M., Martens, M. A., Browning, M., Harmer, C. J., ... & Reinecke, A. (2024). Acute Angiotensin II Receptor Blockade Facilitates Parahippocampal Processing During Memory Encoding in High-Trait-Anxious Individuals. *Biological Psychiatry Global Open Science*, 4(2), 100286.

The overlap between peer-review publication and thesis includes the majority of the methods and results section, as well as brief parts of the introduction and discussion section.

3.1. Introduction

In the previous chapter it was shown that losartan increased PHC, ACC and caudate activity during a memory encoding paradigm. Yet, fMRI data contains more granular information about neural processing than comparing mean brain activity across different conditions. Particularly, in memory research novel multivariate fMRI analyses have been introduced to advance a more nuanced understanding of neural activity during memory formation. Such multivariate analyses investigate spatial brain activity

patterns and their temporal changes, which inherently represents more information than mean signals (Dudai, 2012; Haxby et al., 2001). Thus, using multivariate fMRI approaches in ARB research may present a powerful tool to unravel fine-graded neural underpinnings of ARB modulation during memory encoding and beyond.

3.1.1. Differences between Mean Activity and Activity Patterns

To date, fMRI studies on ARB action – and clinical research more generally – have primarily focused on investigating mean brain activity differences, also known as univariate analyses. The term 'univariate' refers to voxels being treated independently when assessing neural activity, i.e. the activity difference in each voxel is compared between conditions separately. However, more recent multivariate fMRI analyses consider spatial activity patterns across multiple voxels instead, i.e. 'multivariate' refers to multiple (neighbouring) voxels being examined to determine cross-voxel activity patterns for further analysis. Thus, multivariate approaches are often referred to as 'Multivoxel Pattern Analysis' (MVPA; Norman et al., 2006). MVPA most commonly include classifier analysis, representational similarity analysis (RSA) and pattern similarity analysis (PSA).

Classifier analyses use voxel activity patterns to train algorithms and predict specific categorical outcomes, so they are often applied in machine learning (e.g. they answer questions like 'is the presented stimulus an animal or a landscape?'; Cox & Savoy, 2003). On the other hand, RSA and PSA are similar approaches which primarily use correlation-based metrics to track neural activity patterns. More specifically, RSA compares observed voxel activity patterns to a predefined model, which has been typically derived from computational approaches to probe hypotheses on neural representations (e.g. 'how well does my computational model on viewing animals vs landscapes match with the observed neural pattern for viewing animals vs landscapes?'; Kriegeskorte et al., 2008). On the other hand, PSA allows to

analyse temporal changes of voxel activity patterns across time or repetitions (neural stability, e.g. 'does the neural pattern for viewing the same animal change less over time, compared to the neural pattern for viewing the same landscape?'; Xue et al., 2010), and/or to compare activity patterns across conditions (distinctiveness; e.g. 'are different animals processed more similarly to each other than different landscapes?'; LaRocque et al., 2013). Notably, some researchers use the expressions RSA and PSA interchangeably.

To highlight the conceptual difference between univariate fMRI analyses and MVPA, Figure 3.1. illustrates both approaches in a fictive ROI consisting of 10 voxel using the example of PSA. For each of the three events presented in Figure 3.1., an univariate BOLD analysis would compute mean activity across the 10 voxels within this ROI, which is the same for each event in this example (*Mean* = 3). In contrast, PSA would correlate cross-voxel activity between the three events (event 1 and event 2; event 1 and event 3; event 2 and event 3), in which the correlation between 'event 1 and event 2' is higher than the correlation between 'event 1 and event 3'. Such cross-voxel correlation is also referred to as Pattern Similarly (PS). This example clearly shows, that although mean activity across various events may be the same, their pattern similarity may differ. This further highlights that the two approaches measure distinct features of neural activity.

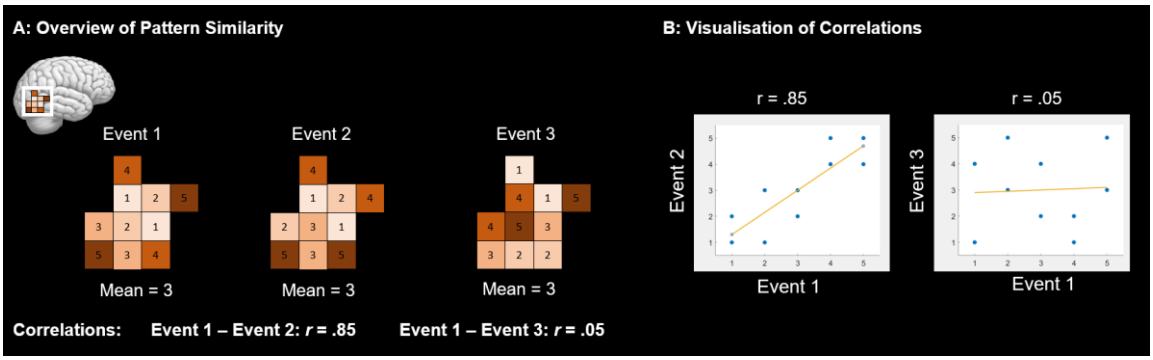


Figure 3.1. Differences between mean activity and Pattern Similarity (PS). A: This example shows voxel activity of a region-of-interest (ROI) for three different events. Each square represents a voxel, while the value inside the square represents their activity. While the mean activity across all three events remains the same within the exemplary ROI, their pattern similarity differs. Pattern Similarity is reflected by the cross-voxel correlation between events. **B:** Visualisation of the correlational analysis underlying this example. The x and y axes contain the voxel values, while each point in the coordinate system reflects a voxel in the ROI.

3.1.2. Different Interpretations of Pattern Similarity

Notably, depending on the definition of the events the interpretation of PS can have a different meaning. That is, PS is considered a measure of neural stability when investigating temporal changes (e.g. Xue et al., 2010), for instance during repeated presentation of the same stimuli (e.g. event 1 and event 2 would be the presentation of the same stimulus, while event 3 would be a different stimulus; Figure 3.2.-A). On the other hand, PS can be considered a measure of distinctiveness, when comparing patterns across conditions (e.g. LaRocque et al., 2013), for instance viewing different animals and landscapes (e.g. all three events are different stimuli, but event 1 and event 2 would be animals, while event 3 would be a landscape; Figure 3.2.-B), or more strikingly viewing stimuli which later will be remembered vs forgotten in a memory paradigm (e.g. all three events are different stimuli, but event 1 and event 2 would be remembered stimuli, while event 3 would be a forgotten stimulus; Figure 3.2.-C).

These different interpretations already hint at one of the striking features of PSA (and RSA): It can be used to investigate activity patterns on a single item level or single trial level, in contrast to univariate approaches (Kriegeskorte et al., 2008). This is because univariate approaches fit one GLM across multiple trials to estimate mean activity changes in response to a specific condition, which results in the loss of trial-specific values. On the other hand, in RSA and PSA each individual item or trial is modelled in a separate GLM, allowing to decode their unique neural pattern (Kriegeskorte et al., 2008). Taken together, RSA and PSA approaches offer a powerful tool to investigate refined questions about the formation of memory traces.

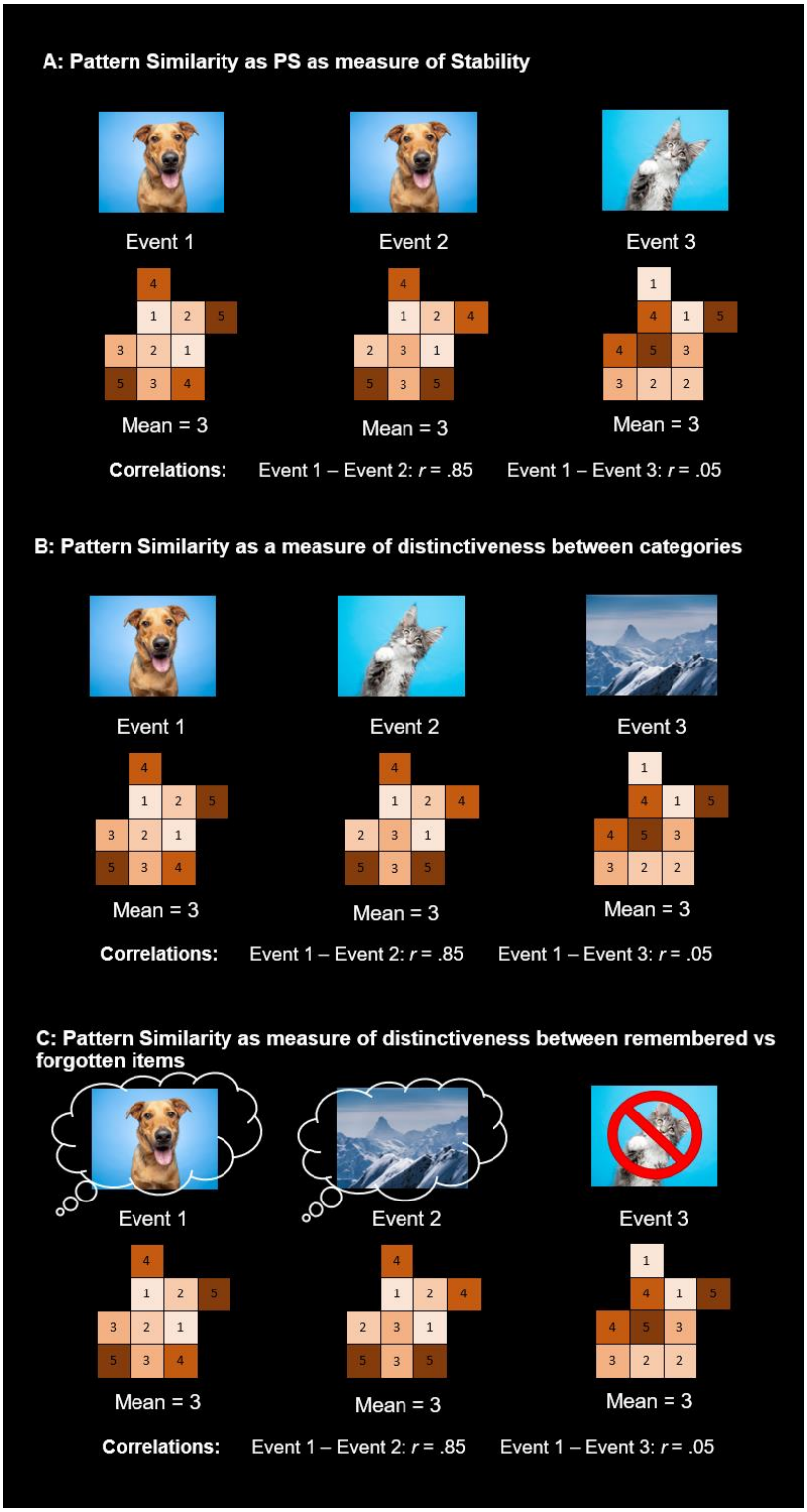


Figure 3.2. Different Interpretations of Pattern Similarity (PS). According to the task applied, PS can be interpreted differently. **A:** PS for a repeated presentation of the same (vs other) item is interpreted as a measure of stability. **B:** PS between the repeated presentation of the same category ('animals') vs other categories ('landscapes') is interpret as category distinctiveness. **C:** PS interpretation of distinctiveness do not only apply to semantic categories, but can also be employed on concepts – such as remembered vs forgotten items.

3.1.3. Using Pattern Similarity to Examine Memory Formation

The item-specific properties made RSA and PSA particularly popular in basic neuroscientific research on learning and memory. So far, promising results on memory formation have been shown, involving the hippocampus and PHC. For instance, previous studies showed that successful memory encoding relies on the formation of stable neural representations of an item reflected by high PS across item repetitions, particularly in memory-related visual processing areas along the ventral visual stream (Xue et al., 2010). Moreover, successful memory encoding may depend on different manifestations of pattern similarity in different brain regions. Specifically, successful memory encoding has been shown to induce high pattern similarity in neocortical areas such as the fusiform gyrus and PHC (LaRocque et al., 2013; Wagner et al., 2016), while neural activity patterns in the hippocampus are typically highly distinct represented by low pattern similarity (Favila et al., 2016; LaRocque et al., 2013). This finding has been suggested to reflect different processes in these areas: Memory traces in higher visual processing areas provide associative networks between different mnemonic events. Hippocampal representations on the other hand are highly specific and discriminate individual memory traces (Sommer & Sander, 2022). Beyond theoretical implications, previous studies further suggested that PSA predicts successful memory formation more accurately than mean activity investigating recollection memory of neutral events and fear expression in classic conditioning paradigms (Hennings et al., 2022; Visser et al., 2013; Xue et al., 2010).

However, despite promising results from basic neuroscience research, MVPA approaches have only begun to be translated into more clinically relevant questions. For example, there is preliminary research showing that PS in the ACC for conditioned stimuli was associated with long-term fear memory and noradrenergic activity, unlike mean BOLD signal (Visser et al., 2015; Visser et al., 2013).

To date, to the best of my knowledge, no study has investigated ARB effects in memory formation using PSA, despite their proposed role in modulating brain activity during memory formation (Xu et al., 2022), and their suggested memory enhancing properties in elderly humans and animals (Bild et al., 2013; Fogari et al., 2003; Fogari et al., 2006). Particularly, since previous research has shown that the neural stability of activity patterns is not only associated with successful episodic memory formation, but might also be a more sensitive neural marker of memory formation compared to mean BOLD signal (Hennings et al., 2022; Visser et al., 2013; Xue et al., 2010). Thus, to complement our univariate results presented in chapter 2 we employed an exploratory PSA to (i) obtain a more granular understanding of the univariate cluster-effects described in chapter 2, and (ii) to further investigate potential influences on the hippocampus as the core brain structure for memory formation.

Due to the novelty in 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 in ARB mechanisms of action on the human memory system.

3.2. Methods and Materials

3.2.1. Participants

The sample remained the same as presented in chapter 2. In brief, it consists of 40 high trait-anxious participants (34 female; losartan n=20, placebo n=20), without a DSM-5 diagnosis and free of CNS-active medication.

3.2.2. Procedure

The study procedure remained the same as presented in chapter 2. In brief, participants were randomly allocated to either a single dose of 50mg losartan or matched placebo, prior to completing a memory paradigm containing

images of animals and landscapes at drug peak level. The main encoding phase of the memory paradigm took place during an fMRI scan. In this phase, participants were presented with images of animals/landscapes, which they had previously encoded pre-fMRI ('familiar' images), and with images of animals/landscapes which they had not previously seen ('novel images'). They were instructed to identify the images as animals/landscapes and to memorise them. Stimulus presentation included a block design of 6 novel and 6 familiar blocks in alternating order. Each block contained images of 4 animals and 4 landscapes (interstimulus interval 500ms). For a detailed overview, see chapter 2 and figure 2.1.

3.2.3. MRI Data Acquisition

MRI data acquisition parameters were the same, as described in the univariate analysis chapter 2 (see 2.2.4.)

3.2.4. MRI Data Preprocessing

Preprocessing steps were similar to univariate analysis presented in chapter 2 (see 2.2.5.). The same steps included BET brain-extraction for structural images, and the following steps for functional images: brain-extraction (BET), motion correction (MCFLIRT), grand-mean intensity normalization, high-pass temporal filtering (cut-off= 90s; Gaussian-weighted least-squares straight-line fitting, sigma = 45s), B0-unwarping and prewhitening (FILM). Notably, in contrast to univariate analysis no spatial smoothing was applied and data remained in native space (Kriegeskorte et al., 2008) to preserve raw voxel activity patterns. That is, while in univariate analysis smoothing is applied to improve signal to noise ratio prior to calculating mean BOLD activity, it would make potential activity differences in neighbouring voxels more uniform. Similarly, transformation into MNI-standard space would apply warping, which may change the included voxels in the ROIs.

3.2.5. Pattern Similarity Analysis (PSA) – First-level analysis

Due to the short interstimulus interval between picture presentations (500ms), this experimental design was not suitable to employ PSA on single-item level as recommended previously (Kriegeskorte et al., 2008). Therefore, PSA was adapted from the single-item/trial design to correspond to the block design in this study. For first-level analyses with FEAT, we used a 3-column format convolved with a gamma hemodynamic response function for the GLM. Following previously published work on single-trial PSA (Hennings et al., 2022; Kriegeskorte et al., 2008; Mumford et al., 2012; Visser et al., 2013; Xue et al., 2010) each block was modelled separately in a GLM, where 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 one contrast 'block of interest>baseline' (for a review of RSA/PSA methodology, see Kriegeskorte et al., 2008), which resulted in 6 first-level GLMs per participant.

3.2.6. Pattern Similarity Analysis (PSA) – Group comparisons

As ROIs, we used the anatomically defined hippocampus by placing a 50% threshold on the Oxford-Harvard subcortical atlas, and each cluster identified in the univariate whole-brain analysis. The two PHC clusters were combined into a single ROI. Since the functional MRI data remained in native space to preserve raw voxel activity patterns, the ROIs were registered from MNI standard space into each subject's native space using FNIRT, prior to group analyses.

For the following group-level analyses custom MATLAB code was used based on the established protocol of RSA/PSA analysis (Kriegeskorte et al., 2008). For each ROI and each first level GLM (which represent the block of interest), voxel values were extracted to create a vector, in which each value corresponds to activity at a specific voxel location. Per participant, this

resulted in 12 vectors per ROI corresponding to each block (6 novel, 6 familiar). Within each ROI, pattern similarity (PS) between blocks was calculated across voxel activity vectors using Fisher z-transformed spearman correlations (Kriegeskorte et al., 2008). This leads to a PS score per block and participant, which can be illustrated in a Pattern Similarity Matrix (PSM; for an exemplary participant see figure 3.3.). We then calculated the mean PS for each condition (familiar-familiar, novel-novel) for each participant. To test for group differences in mean PS between losartan and placebo, a group (losartan, placebo) x condition (familiar-familiar, novel-novel) mixed-model ANOVA was conducted.

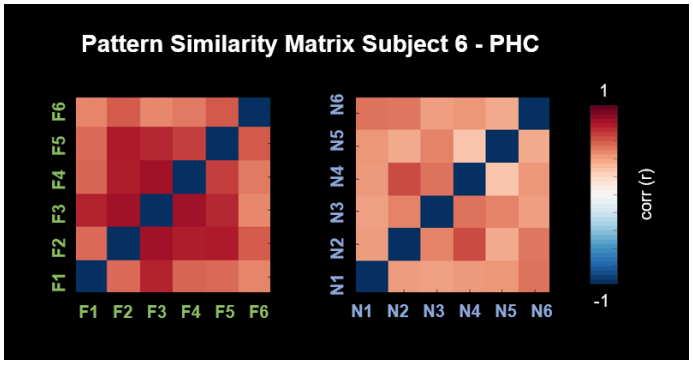


Figure 3.3. Exemplary Pattern Similarity Matrix (PSM) of subject 6 in the parahippocampal gyrus (PHC). The colours represent the cross-voxel correlation across the familiar (green font) and novel (blue font) blocks. Higher correlations represent higher Pattern Similarity.

3.3. Results

3.3.1. Notes regarding Interpretation of Pattern Similarity

We conducted PSA to explore whether the ARB 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. As we employed PSA on a block level, PS reflected the neural stability of a *cognitive process* rather than neural

stability of an *item representation* when employed on a single trial/item level (for more information on PS interpretation, see Kriegeskorte et al., 2008). PS interpretation reflects stability here since temporal changes of voxel activity patterns are compared in response to being repeatedly demanded the same cognitive process (i.e. viewing the same familiar images; vs. viewing/encoding novel images).

3.3.2. PSA in Response to Novel vs Familiar Images across Groups

During memory encoding PS differed for novel and familiar blocks across groups. PS was higher for novel compared to familiar blocks in all identified clusters: PHC (novel: M=.65, SD=.22; familiar: M=.46, SD=.16), ACC (novel: M=.23, SD=.09; familiar: M=.19, SD=.10), caudate (novel: M=.22, SD=.09; familiar: M=.18, SD=.07), as well as the anatomically defined hippocampus (novel: M=.27, SD=.11; familiar: M=.19, SD=.09), all $F(1,38)>6.67$, all ps<.014, all $\eta_p^2>.15$ indicating more stable memory formation processing for novel compared to familiar images (figure 3.4.).

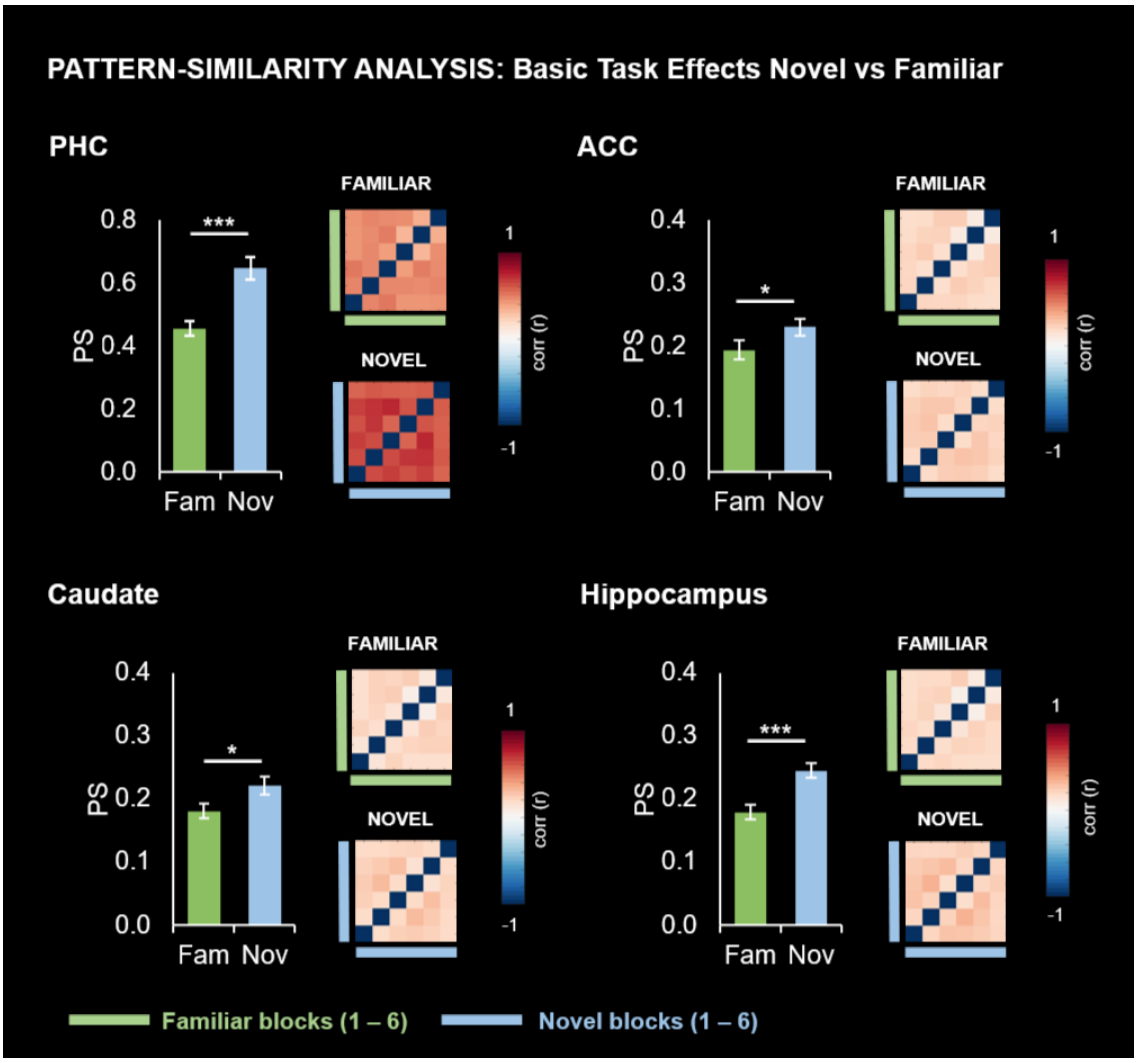


Figure 3.4. Pattern-Similarity Analysis (PSA) of the basic task effect. The regions are based on the univariate whole-brain clusters presented in chapter 2, i.e. parahippocampal gyrus (PHC), anterior cingulate cortex (ACC) and caudate, in addition to the anatomically defined hippocampus. The matrices 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 is calculated for each condition (novel, familiar) resulting in the bar plots. Across all regions PS is higher for novel compared to familiar images.
*** $p < .001$, * $p < .05$

3.3.3. Losartan effects on multivariate PSA – Regions of Interest

Losartan administration changed the neural stability during memory formation reflected by PS. In the PHC, losartan induced higher PS for novel and familiar blocks (novel: losartan *M*=.75, *SD*=.19, placebo *M*=.55, *SD*=.21; familiar: losartan *M*=.53, *SD*=.13, placebo *M*=.38, *SD*=.14; main effect group

$F(1,38)=12.95$, $p<.001$, $\eta_p^2=.25$; figure 3.5.), indicating higher neural stability in processing both, already encoded familiar images and not previously seen novel images. There was no image condition x group interaction effect ($F(1,38)=1.09$, $p=.30$, $\eta_p^2=.03$).

In the ACC, there was a significant image condition x group interaction effect ($F(1,38)=7.07$, $p=.01$, $\eta_p^2=.16$), with the losartan group showing lower PS for familiar blocks compared to placebo (losartan $M=.16$, $SD=.08$, placebo $M=.23$, $SD=.11$, $t(38)=2.27$, $p=.03$, $d=.72$), but no PS difference for novel blocks (losartan $M=.23$, $SD=.09$, placebo $M=.23$, $SD=.09$, $t(38)=-.23$, $p=.82$, $d=-.07$), suggesting that losartan reduced neural stability when processing already encoded familiar images but has no effect on neural stability when processing not previously seen images.

There were no group differences in the caudate and hippocampus ROIs (all ps>.29, figure 3.5.).

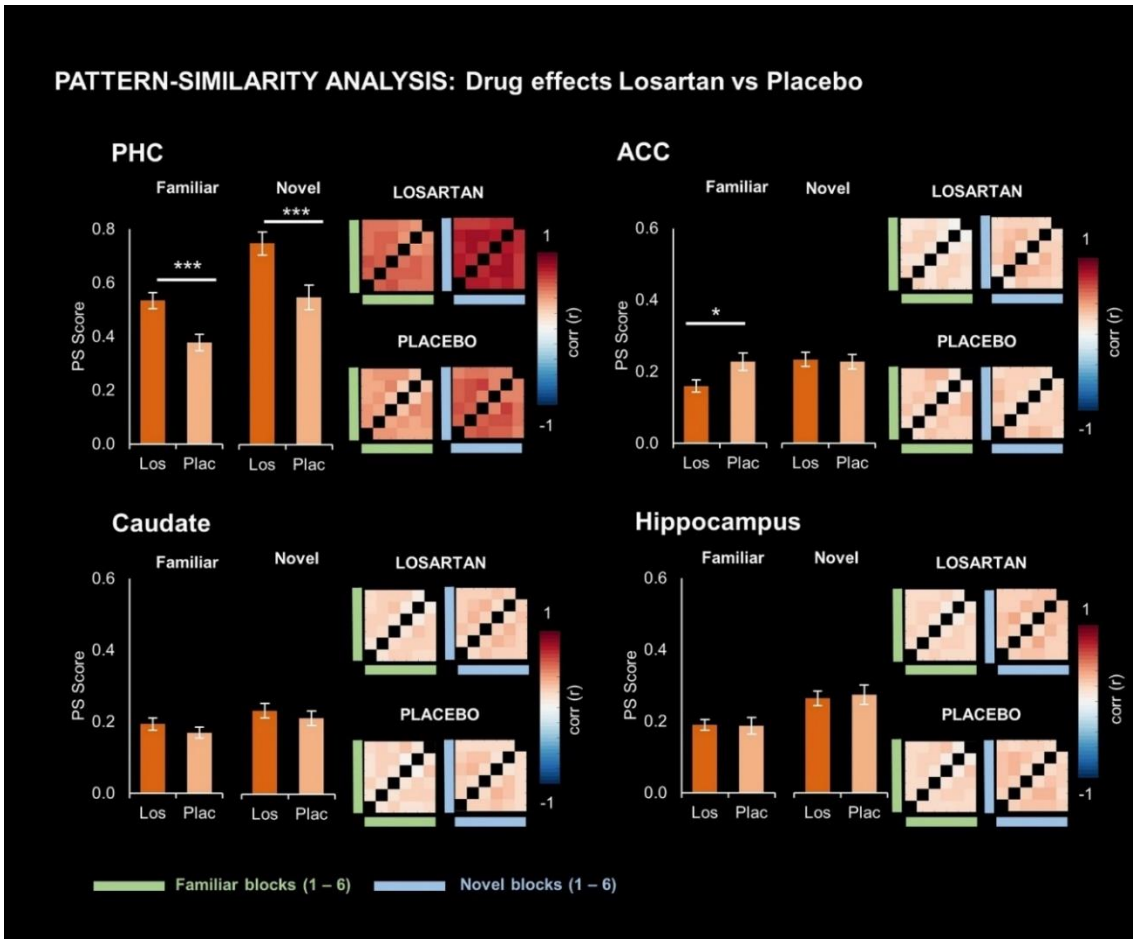


Figure 3.5. Pattern-Similarity Analysis (PSA) Drug Effects, based on the univariate whole-brain clusters parahippocampal gyrus (PHC), anterior cingulate cortex (ACC), caudate and anatomically defined hippocampus. The matrices represent the pattern similarity (PS) scores, i.e. correlated cross-voxel activity between each block, where higher correlations represent higher PS. The mean PS Score is calculated for each condition (novel, familiar) and group (losartan, placebo) resulting in the bar plots. The losartan group has greater PS for novel (blue) and familiar (green) images in the PHC, respectively. In contrast, in the ACC, the losartan group shows lower PS. No group differences were found in the caudate and hippocampus. *** $p < .001$, * $p < .05$

3.4. Discussion

This chapter investigated the effects of ARBs on neural memory encoding using PSA to advance a more granular understanding of neural ARB action by complementing the univariate analyses presented in chapter 2. In this exploratory approach, our results show that during memory formation a single dose of losartan increased the neural stability for novel and familiar

images in the PHC, while decreasing the neural stability of familiar images in the ACC. Across groups (losartan and placebo), neural stability was higher for novel compared to familiar images overall.

This is the first experimental study to date, to the best of my knowledge, using PSA to investigate central ARB action during memory formation. Instead of averaging BOLD signal across voxels, PSA allows to analyse temporal changes in the stability of fine-grained spatial activity patterns within a brain area, which intrinsically captures a greater richness of information than mean activity analyses (Dudai, 2012; Haxby et al., 2001). While previous studies have primarily used PSA on item/trial level to understand single item representation over time, we employed such an approach in a block design, allowing to draw conclusions about the neural stability of a cognitive process ('cognitive stability') rather than a single item representation ('item stability").

3.4.1. Greater Pattern Similarity – A Measure of Cognitive Stability

Overall, our results showed that PS was higher for novel blocks (not previously seen images) compared to familiar blocks (already encoded images). This is in line with previous research showing that greater item-stability occurs in a variety of brain regions during memory encoding, most typically involving the hippocampus, PHC and prefrontal regions (Xue et al., 2013; Xue et al., 2010). We extend these finding by demonstrating that higher cognitive stability is also related to active memory encoding.

Interestingly, PS for novel images was higher across all ROIs, even those outside the memory network (i.e. ACC and caudate). This may be due to the fact that the presentation of novel images was a more cognitive demanding task, in which all participants were instructed to memorise the images, alongside identifying them as animals/landscapes. In contrast, being presented with familiar images only required the identification as

animals/landscapes since images were already encoded pre-fMRI. Thus, higher PS for novel images in the caudate and ACC may reflect increased attentional engagement and decision-making, particularly since the ACC and caudate have been implicated in those processes (Arcizet & Krauzlis, 2018; Ding & Gold, 2010; Ding & Gold, 2012; Newman & McGaughy, 2011; Segalowitz & Dywan, 2009). For instance, the ACC is involved in various aspects of attentional control, primarily surrounding attention to emotional stimuli and during conflicting task-demands (Newman & McGaughy, 2011; Segalowitz & Dywan, 2009), but also more generally during sustained attention (Newman & McGaughy, 2011). On the other hand, while the caudate has been implicated in perceptual decision making (Ding & Gold, 2010; Ding & Gold, 2012), there is preliminary evidence showing that this may be underpinned via visual attention during decision-making (Arcizet & Krauzlis, 2018).

Conceptually, the overall increase in PS for novel compared to familiar blocks is particularly interesting, given that a higher PS for familiar blocks would be expected from an item representation perspective, while from a cognitive process perspective this is not necessarily the case. To illustrate, during familiar blocks the same images were repeatedly presented. Thus, familiar blocks contain the same visual features each time, while novel blocks do not. If PS would purely reflect item representations (and there were no changes in the involved cognitive process) it would imply that the neural stability for familiar blocks should be higher, simply because the same visual features were processed in each block (Xue et al., 2010). However, our findings reveal the opposite pattern. Our PS results showing increased neural stability for novel compared to familiar blocks in all ROIs (involving both the memory network and supporting attentional structures), suggest that PS may effectively reflect the stability of a cognitive process.

3.4.2. Implications of ARBs increasing Cognitive Stability in the PHC

Moving on to ARB effects, univariate analyses in chapter 2 showed that losartan induced higher BOLD signal in the PHC. In addition, PSA further revealed that information processing in the PHC was more stable across blocks following losartan, as reflected by higher PS. These results align with previous research underlining the role of the PHC for successful memory formation of scene images. These studies showed that mean activity in the PHC was higher for subsequently remembered than not-remembered scene images (Staresina et al., 2011). Accordingly, three previous experiments (Xue et al., 2010) showed that item stability in the PHC over repeated stimulus presentation, alongside higher mean activity, was associated with successful memory encoding. Moreover, PS between different items in the PHC was higher for remembered than not-remembered items. PHC processing during memory encoding has been suggested to reflect the formation of memory traces particularly representing visual information of an event. That is, during memory retrieval, previous studies showed memory reinstatement in the PHC reflected by increased PS between encoding and retrieval of the same images (Ritchey et al., 2013; Staresina et al., 2012). Memory reinstatement in the PHC also expand to more naturalistic film material underlining the role of the PHC for autobiographical memory retrieval (Chen et al., 2017; Oedekoven et al., 2017). Collectively, these studies support the role of the PHC as part of the memory network. Thus, such previous work associating PS in the PHC with successful memory encoding, may suggest that our PSA results imply ARB-induced improvements in memory performance. Particularly, as memory enhancing effects have been previously shown in behavioural studies with elderly humans after ARB intake (Fogari et al., 2003; Fogari et al., 2006). However, since there were no behavioural effects of losartan on memory performance in this study, potential implications about memory enhancing effects remain speculative

at this point and need to be re-examined in future studies (see chapter 2.4. for detailed discussion).

In contrast to the PHC, losartan did not influence cognitive stability in the hippocampus, which is in line with our univariate analyses in chapter 2. Thus, our PSA results continue to underline that within the memory network, ARBs may particularly affect higher-order visual processing through parahippocampal modulation, instead of having direct hippocampal effects. This idea is further supported by the fact that increased cognitive stability was shown for both – novel and familiar images. Similar to the discussion in chapter 2, a memory effect would have required a distinct ARB effect on novel vs familiar images, since familiar images have already been encoded pre-fMRI.

Notably, our results indicate that PSA might be a more sensitive marker to capture targeted ARB effects on the memory network, compared to univariate BOLD analysis: while PSA showed that neural processing is specifically more stable in the memory network (PHC), it is either less stable (ACC) or not affected (caudate) outside the memory network. In contrast, analyses in chapter 2 showed that the BOLD signal increased in clusters within the memory network (PHC) and outside the memory network (ACC, caudate). Overall, our combined fMRI results showed that PHC activity not only increased (chapter 2) but also became more stable following angiotensin-II receptor blockade.

Outside the memory network, losartan decreased the cognitive stability for familiar images in the ACC. This is particularly interesting, as univariate analyses in chapter 2 showed that losartan administration *increased* ACC activity for familiar images. Since the ACC is part of the limbic system, it has strong connections to the amygdala and it is involved in variety of emotion regulation processes and fear conditioning (Etkin et al., 2011). Notably, structural and functional alternations in the ACC have also been associated

with PTSD (Jhang et al., 2018). Nevertheless, beyond its role within the limbic system, the ACC has been implicated in long-term memory recall in rodent studies due to interactions with the hippocampus (Makino et al., 2019; Wirt & Hyman, 2019), although its role is not fully understood yet. On the other hand, the ACC in humans has primarily been implicated in fear memory (Etkin et al., 2011), and there is first evidence from PSA approaches supporting this proposed role. In these studies, it has been shown that higher PS in the ACC for the CS+ predicted later fear responses (Visser et al., 2013). Similarly, it was shown that higher PS in the ACC for CS+ correlated with noradrenergic activity and fear response (Visser et al., 2015). However, it is difficult to compare these results to the current study, since the current study used neutral material to investigate episodic memory rather than investigating fear learning. Similarly, previously published PSA findings on general memory formation do not commonly include the ACC.

3.4.3. Limitations

The study described in this chapter has some limitations, beyond those described in chapter 2. Although results indicated higher PS for novel compared to familiar images, in line with previous research showing higher PS during memory encoding (Xue et al., 2010), we cannot investigate item-specific effects due to the short, fixed interstimulus interval (500ms) in this block-design. As a result, we further cannot differentiate the neural stability between correctly remembered and forgotten items using PSA, which might at least partially explain the lack of ARB effects on the hippocampus. Hence, our task might not be sensitive enough for fine-graded memory analysis by not taking advantage of PSA's full analysis potential. Future studies might wish to consider this at their study design stage.

3.4.4. Pattern Similarity Analysis: A Powerful Tool for Clinical Research?

This study has taken a first step to apply MVPA approaches, in particular PSA, to clinically relevant research questions regarding memory formation. Even beyond memory formation, multivariate PS offers a powerful tool for clinical research to unravel neural activity patterns underlying representations of abstract information during a cognitive process and psychiatric symptoms (Nour et al., 2022). For instance, PSA can be used to investigate other domains in which ARBs have been shown to modulate neurocognitive processes – particularly in fear learning paradigms. To illustrate, future studies could examine the voxel activity patterns for a threat cue, a safety cue and various ambiguous cues resembling the threat/safety cues to various degrees (e.g. similar to approaches where faces of neutral and emotional expressions were morphed to various degrees, see Harmer et al., 2003). For instance, during the first phase of such task, participants would be presented with the threat cue (followed by an aversive stimulus) and a safety cue (no aversive stimulus). In the second phase of the task, participants would be repeatedly presented with the threat cue, the safety cue, and ambiguous cues to rate their expectancy of an aversive stimulus to follow (but no aversive stimulus will occur). Using PSA, it could be examined which degrees of ambiguous cues share more similar neural activity patterns to the threat cue or safety cue, and whether ARBs (or clinical conditions) modulate such PS. This would offer the unique opportunity to specifically track how ambiguous cues are represented in the brain, which would be particularly relevant in PTSD, since PTSD has been linked with reduced threat/safety differentiation (Garfinkel et al., 2014; Jovanovic et al., 2012). In fact, in a similar investigation it has been recently shown that higher PS between ambiguous faces and unthreatening faces was associated with reduced anxiety symptoms in young adults (Saragosa-Harris et al., 2023). While fear learning is just an example, PSA approaches would offer a great opportunity

to probe additional clinical theories, such as attention biases and interpretation biases in psychopathology. In fact, in a recent review it has been raised that the use of MVPA approaches is important to progress with neurosciences-informed clinical research, since it has been stagnating in its overarching goal to unravel biomarkers and/or robust mechanistic neural pathways for psychiatric disease and treatment response (Nour et al., 2022).

In conclusion, this study took a first step to establish the use of MVPA, in particular PSA, to investigate ARB-modulated memory formation. Our results showed that ARBs increase neural stability within the memory network (PHC), while decreasing neural stability outside the memory network (ACC). Yet, trial-specific examinations (e.g. between remembered and forgotten items), remain to be investigated to specifically probe successful memory effects. Moving forward, it is important to establish a regular use of approaches like PSA in clinical research, beyond memory formation.

4

Chapter 4
The effects of ARBs on Resting State Functional Connectivity

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Key abbreviations

DMN: Default Mode Network

FPN: Frontoparietal Network

ICA: Independent Component Analysis

rsFC: Resting State Functional Connectivity

RSN: Resting State Network

SN: Salience Network

The Effects of ARBs on Resting State Functional Connectivity

Following task-related neural modifications, Chapter 4 explores the broader impact of losartan on the brain's intrinsic organisation using resting-state functional connectivity. Since resting state functional connectivity is task-independent it has the potential to serve as a biomarker for psychiatric disease in general – and for PTSD specifically. Using a complementary approach of data-driven independent component analysis alongside hypothesis-driven seed-based analyses, this chapter focuses on neural networks and brain areas, which are pivotal for cognitive and emotional processing implicated in PTSD.

4.1. Introduction

There is increasing evidence that the renin-angiotensin-system (RAS) plays an important yet underestimated role in the development and treatment of anxiety and posttraumatic-stress disorder (PTSD). Drugs targeting the RAS, such as 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). Similarly, ARB administration has been shown to enhance fear extinction in experimental studies (Marvar et al., 2014; Zhou et al., 2019), which is the key mechanisms underlying exposure therapy – the gold standard for anxiety and PTSD treatment (Bisson et al., 2013; Lewis et al., 2020).

However, the neural underpinnings of such effects remain only poorly understood, due to a predominance of animal research which provides valuable insights into precise receptor-mediated effects but lacks the capability for direct brain imaging – a crucial component for human

translation. Initial evidence from human task-based brain imaging studies suggests that ARBs, such as losartan, influence a variety of neurocognitive processes related to emotional response and memory – both domains in which aberrations have been linked to PTSD development (Brewin, 2014; Ehlers & Clark, 2000; Kunimatsu et al., 2020). For instance, previous research has shown that a single dose of losartan improved differentiation of fearful and happy facial expressions in the amygdala (Reinecke et al., 2018). During a memory task losartan enhanced processing in the parahippocampal gyrus (Shkreli et al., 2024), a region implicated in higher-order visual processing and memory encoding (Aminoff et al., 2013; Eichenbaum & Lipton, 2008). Additionally, the drug reduced coupling between the hippocampus and the amygdala during memory encoding of negative images (Xu et al., 2022). Yet, it remains unknown to what degree such task-dependent effects result from an ARB-induced modulation of the intrinsic organisation of the brain's fear and memory network. This is particularly relevant to investigate given the widespread expression of angiotensin-II receptors in core areas for neurocognitive processing such as the amygdala and hippocampus (von Bohlen und Halbach & Albrecht, 2006).

4.1.1. Investigating the Brain's Internal Organisation at Rest

A powerful tool to understand the brain's intrinsic organization is the examination of resting state functional connectivity (rsFC). This approach captures spontaneous fluctuations in brain activity, since the brain remains active and interconnected in the absence of external stimuli or directed tasks (Fox & Raichle, 2007; Smith et al., 2009). Importantly, intrinsic rsFC brain organisation aligns with functional networks involved in task-based studies (Cole et al., 2014; Salvo et al., 2021; Smith et al., 2009). Thus, rsFC allows to investigate whether brain regions implicated in PTSD pathogenesis and responsive to ARB action during task performance – such as the amygdala, hippocampus and PHC – are also modulated in their intrinsic connectivity

at rest. Further, rsFC is becoming an increasingly popular approach for clinical research due to its task-independence. That is, rsFC not only facilitates direct comparisons between study results but may also be used as a biomarker for psychopathology or treatment response.

4.1.2. Resting State Functional Connectivity in PTSD – Core Areas

So far, localised rsFC alterations in PTSD have been prominently investigated in the amygdala, (anterior) insula and hippocampus ROIs (commonly known as 'seed regions' in rsFC literature), due to their crucial role in fear processing and memory formation. In these studies, PTSD and posttraumatic symptom severity have been associated with increased rsFC between the amygdala and insula (Dager et al., 2019; Rabinak et al., 2011; Sripada et al., 2012) alongside inconsistent results on the rsFC of the amygdala with prefrontal regions and anterior cingulate cortex (ACC) (V. M. Brown et al., 2014; Duan et al., 2014; Rabinak et al., 2011; Sripada et al., 2012). Similarly, with respect to the hippocampus, widespread clusters were associated with PTSD, including decreased rsFC between hippocampus and dorsomedial PFC (Metz et al., 2019), increased rsFC between the posterior hippocampus and posterior cingulate cortex (Malivoire et al., 2018), decreased rsFC between the hippocampus and amygdala (Sripada et al., 2012), as well as increased rsFC between the hippocampus and inferior frontal gyrus (Sheynin et al., 2020).

4.1.3. A network perspective into Resting State Functional Connectivity

Given that the brain is organized into intrinsic resting-state networks (RSNs; (Damoiseaux et al., 2006; Fox & Raichle, 2007), solely investigating rsFC of brain structures guided by task-based hypotheses (e.g. amygdala, hippocampus and parahippocampus in ARB research) might hinder a

comprehensive understanding of the intricate dynamics of rsFC. RSNs have been consistently replicated across studies and involve prominent networks such as the default mode network (DMN), salience network (SN), and frontoparietal network (FPN), which is also known as the executive control network (Damoiseaux et al., 2006; Fox & Raichle, 2007; Seeley et al., 2007). For instance, the DMN includes the posterior cingulate cortex, precuneus and ventromedial prefrontal cortex, and it is implicated in self-referential processing, mind-wandering and autobiographical memory (Raichle, 2015). On the other hand, the SN is composed of structures such as the insula, ACC and inferior frontal gyrus. It is involved in attentional and interoceptive processing to ensure adequate detection and adaptive behavioural response to salient stimuli (Menon & Uddin, 2010; Seeley et al., 2007). The FPN is responsible for executive functions, such as goal-directed behaviour and top-down control, and includes the DLPFC and the lateral parietal cortex (Seeley et al., 2007). In addition to these core RSNs, there are also less prominent but noteworthy networks for example the auditory network, sensory-motor network and cerebellar network (Damoiseaux et al., 2006; Fox & Raichle, 2007).

4.1.4. Resting State Networks Implicated in PTSD

From a RSN perspective, PTSD has been linked most confidently to changes in rsFC within the DMN and SN (Harnett et al., 2021; Koch et al., 2016; Vanasse et al., 2019; Weng et al., 2019). In particular, it has been shown that PTSD diagnosis and posttraumatic stress symptoms were associated with greater intra-network connectivity within the SN (Koch et al., 2016; Sheynin et al., 2020; Sripada et al., 2012), but see (Liu et al., 2017; Zhang et al., 2015), and increased inter-network connectivity between the SN and DMN (Lanius et al., 2010; Sheynin et al., 2020; Sripada et al., 2012; Zhang et al., 2015). On the other hand, the intra-network connectivity within the DMN is reduced (Akiki et al., 2018; Koch et al., 2016; Liu et al., 2017; Sheynin et al., 2020;

Sripada et al., 2012; Viard et al., 2019). Initial evidence also suggests PTSD-related rsFC changes in the FPN (Akiki et al., 2018; Vanasse et al., 2019; Vuper et al., 2021), including decreased intra-network rsFC (Akiki et al., 2018), decreased FPN-cerebellum rsFC (Vuper et al., 2021), and a more diffuse pattern for example showing an increased rsFC between the FPN the ACC and a decreased rsFC between the PFN and the insula (Vanasse et al., 2019).

4.1.5. Two Complementary Approaches to Investigate Resting State Data

To investigate rsFC changes in pre-defined regions and RSNs two popular methodological approaches are commonly used: seed-based analyses and independent-component-analysis (ICA; for review, see van den Heuvel & Hulshoff Pol, 2010). Both approaches are based on the general assumption of statistical dependency between time series of interconnected brain regions reflecting their simultaneous activation. While seed-based analyses involve the hypothesis-driven selection of a pre-defined ROI as 'seed' region, ICA-based approaches are data-driven and do not involve a priori hypotheses to select brain regions (van den Heuvel & Hulshoff Pol, 2010). Instead, ICA-approaches decompose spontaneous brain activity signal into distinct RSNs containing *multiple regions* allowing to investigate RSNs in their entirety (Beckmann et al., 2005).

4.1.6. The Current Study

Although ARB action modulates brain structures involved in PTSD pathogenesis during task performance – such as the amygdala and hippocampus –, and although rsFC changes in these brain structures have been shown in PTSD patients, no study has investigated the effects of ARBs on rsFC. Notably, previous research suggests that PTSD symptom improvement is associated with normalisations of rsFC patterns (Abdallah et

al., 2019; Vuper et al., 2021), so that ARB effects may potentially tackle PTSD-related rsFC aberrations at an early stage. Thus, this study aimed to investigate the effects of one dose of the ARB losartan on rsFC in brain structures and RSNs implicated in PTSD.

To enhance the robustness and depth of these insights within the complex dynamics of rsFC, we employed a complementary approach of seed-based analysis and data-driven ICA.

The seed selection was informed by previous rsFC studies in PTSD, which largely correspond to (i) ARBs receptor expression in core limbic and memory network areas (von Bohlen und Halbach & Albrecht, 2006) and (ii) task-based research on central ARB action involving the fear and memory network. That is, previous rsFC studies in PTSD have shown rsFC changes in the amygdala, (anterior) insula and hippocampus (Dager et al., 2019; Malivoire et al., 2018; Metz et al., 2019; Rabinak et al., 2011; Sripada et al., 2012). Similarly, task-based ARB research has demonstrated modulatory effects in the fear network including the amygdala (Reinecke et al., 2018), and additional modulatory effects in the memory network – in particular the hippocampus (Xu et al., 2022). Although PHC seeds have not been examined in PTSD-related rsFC studies yet, chapter 2 and chapter 3 have consistently shown ARB modulations in this brain region, prompting the decision to include rsFC analysis of the PHC into this study.

Taken together, seed-based analyses in this study included the amygdala and anterior insula as structures within the fear network, and they included the hippocampus and PHC as structures within the memory network. To ensure a holistic examination based on the core neurocognitive manifestations in PTSD (see chapter 1.3), and the lack of targeted ARB research, we further included an exploratory vmPFC seed-analysis due to its crucial role in response inhibition and dysfunctions previously reported in PTSD (DeGutis et al., 2015; Hayes et al., 2012; Hughes & Shin, 2011).

Given that PTSD has been primarily associated with increased rsFC within the SN (Koch et al., 2016; Sheynin et al., 2020; Sripada et al., 2012; Vanasse et al., 2019), decreased rsFC within the DMN (Akiki et al., 2018; Koch et al., 2016; Liu et al., 2017; Sheynin et al., 2020; Sripada et al., 2012; Viard et al., 2019) and initial evidence of decreased rsFC within FPN (Akiki et al., 2018), we expect that a single dose of losartan leads to decreased rsFC within the SN, increased rsFC within the DMN, and increased rsFC within the FPN.

4.2. Methods and Materials

4.2.1 Participants

45 high-anxious participants (age 18 to 45) were included in this study. They represent a subsample of the fMRI participants in chapter 2 and 3 (n = 16), and a subsample of participants acquired as part of a different study which was not within the scope of this DPhil (n=29; Reinecke et al., 2018). Inclusion criteria was consistent for both studies and comprised of participants aged 18 to 50, presenting with a score of 40 or higher on the trait subscale of the State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983) and not meeting criteria for a current psychiatric disorder as assessed by the Structured Clinical Interview for DSM-IV (First & Gibbon, 2004) and DSM-V (First et al., 2016). Participants also had to be free from CNS-active medication for at least 6 weeks, have a body mass index of (BMI) of 18-30 kg/m^2, be right-handed, have no contraindication to MRI, and have no first-degree family member with a history of a severe psychiatric disease. Both studies were approved by the Oxford University research ethics committee (ethics reference: R58494/RE004 and MSD-IDREC-C3-2015-832), and all participants gave written informed consent.

4.2.2. Procedure

Eligibility for the study was assessed through an online screening. To characterise the sample, participants completed the Anxiety Sensitivity Index Revised (ASI-R; Taylor & Cox, 1998), the neuroticism subscale of the Eysenck Personality Inventory Revised (EPQ-N; Eysenck & Eysenck, 1975), the Behavioural Inhibition and Activation Scale (BIS/BAS; Carver & White, 1994), the Beck Depression Inventory (BDI; Beck et al., 1996), and the Attentional Control Scale (ACS; Derryberry & Reed, 2002). Prior to the testing session, participants were stratified for gender and randomly allocated to one of two drug conditions in a double-blind design: losartan (Cozaar, Merck Sharp & Dohme Ltd.) to be given as a single oral 50mg dose or matched placebo (microcrystalline cellulose; Rayotabs, Rayonex GmbH), both over-encapsulated by an independent researcher to look identical. Randomisation was conducted in blocks of four with a sequence created using a random number generator (random.org).

On the testing day, to assess potential changes in subjective state mood and physiological symptoms, participants completed visual analogue scale ratings before drug administration and at drug peak time which is 1hr after drug administration (Lo et al., 1995; Ohtawa et al., 1993). Similarly, heart rate and blood pressure were measured at these two timepoints via an Omron 705IT sphygmomanometer.

Scanning began ~1.5 hours after drug administration. During the scan participants were presented with a fixation cross in dimmed light. They were instructed to look at the fixation cross, to think of nothing in particular, and to not fall asleep.

At the end of the testing session, both participant and experimenter were asked to guess whether the participant had received losartan or placebo.

4.2.3. Resting State Image Acquisition

Brain imaging data was acquired for 29 participants using a 3T Siemens MAGNETOM TrioTim scanner (Centre for Clinical Magnetic Resonance Research), and for 16 participants using a 3T Siemens MAGNETOM Prisma scanner (Centre for Human Brain Activity). Imaging data was preprocessed and analysed using FSL (FMRIB Software Library; www.fmrib.ox.ac.ul/fsl).

Resting-state functional images were acquired a using a gradient echo EPI sequence and the following parameters: 119x192x192 field of view acquisition matrix, flip angle=89°, voxel resolution = 3×3×3.5 mm, repetition time (TR)=2000ms, echo time (TE)=28ms, number of volumes=180, acquisition time = 6 min 4 sec. 3D high-resolution T1-weighted images were acquired using an MPRAGE sequence with the following parameters: 174x192x192 field of view matrix, flip angle = 8°, voxel resolution 1mm^3, TR=2040ms, TE=4.7ms, inversion time (TI)=900ms, acquisition time = 5 min 56 sec. 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.

4.2.4. fMRI data Pre-Processing

fMRI data was pre-processed using McFLIRT motion correction (Jenkinson et al., 2002), BET brain extraction (Smith, 2002), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, highpass temporal filtering using a cut-off value of 150s (Gaussian-weighted least-squares straight line fitting, with sigma=75.0s), B0-unwarping through the acquired fieldmap images, spatial smoothing using a Gaussian kernel of 5mm 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 Beckmann et al., 2005). Subsequently, the

identified components were automatically classified into signal and noise components using a standard training dataset within FMRIB's ICA-based Xnoiseifier (FIX), which regresses out the signal of artefactual components reflecting non-neuronal fluctuations (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Preprocessed and 'cleaned' functional data was then registered to the individual's structural scan using FLIRT and to the standard space using FNIRT optimized by the boundary-based-registration (BBR) approach.

4.2.5. ICA-Group Analysis

In order to identify large-scale patterns of functional connectivity in the population of subjects, fMRI data was temporally concatenated across all subjects prior to being decomposed into independent components (ICs) using MELODIC (Beckmann et al., 2005). In line with previous work, dimensionality estimation for the number of group map components within the MELODIC function was set to 25 (e.g. Filippini et al., 2009; Martens et al., 2022). Subsequently, the 25 identified ICs were classified as meaningful RSNs or noise components by visual inspection and by comparison to previously published maps (Smith et al., 2009).

To assess groups differences in RSN connectivity the 'dual regression' approach was used which allows for voxel-wise comparisons of rsFC and consists of three stages. This involves (i) a multivariate spatial regression for each subject in which all 25 identified group-IC spatial maps were fitted by a linear model into the subject's preprocessed 4D functional data, resulting in individual time series maps for each component for each subject. Following, (ii) a multivariate temporal regression was conducted in which each of these subject-specific time series maps was fitted by a linear model into the same preprocessed 4D functional data of each subject, which resulted in subject-specific spatial maps.

Finally, (iii) the subject-specific spatial maps were concatenated across subjects into single 4D files (one per original IC map, with the 4th dimension being subject ID), which were the basis for statistical testing on potential group differences. To assess group differences for each meaningful group-IC representing an RSN, a general linear model (GLM) was fitted using the permutation-based approach within the randomise function (5000 permutations), at alpha-level $p<0.05$ and a threshold-free cluster enhancement (TFCE) correction for multiple comparison. The GLMs included two regressors of interest (losartan, placebo), as well as individual structural grey matter maps to correct for potential volumetric differences. Taken together, this results in individual spatial maps per RSN characterizing group differences in rsFC.

4.2.6. Seed-based Group Analysis

Bilateral seeds were anatomically defined based on a 50% threshold on the Oxford-Harvard subcortical atlas. Seeds comprised of the amygdala, hippocampus, anterior insula, anterior PHC and posterior PHC. The separation of the PHC into the anterior and posterior PHC was also based on the Oxford-Harvard subcortical atlas, in which they are defined as anatomically distinct regions, potentially through the large size of a combined, single PHC ROI. To divide the anterior part of the insula from the posterior part of no interest, the insula mask was split at MNI y=0 in line with previously published studies (Geuter et al., 2017; Ploner et al., 2011).

As there was no anatomical definition of the vmPFC in the Oxford-Harvard subcortical atlas, the bilateral vmPFC seed was created using a 6mm sphere on the MNI voxel-coordinates (2, 46, -8) and (-2, 46, -8) (Felger et al., 2016). To prepare first-level seed-based analysis, seeds were transformed from MNI standard space into EPI subject space via non-linear registration prior to extracting their subject-specific timeseries. To control for temporal fluctuations which may arise through white matter (WM) and cerebrospinal

fluid (CSF) noise over the course of scanning, subject-specific masks for WM and CSF were created through non-linear registration from MNI standard space WM and CSF masks, accordingly. Subsequently, the subject-specific timeseries of WM and CSF were extracted.

First-level analyses were carried out using FEAT to detect which voxels were correlated to the time-series of the seed regions. One GLM per seed region was fitted, which included the regressor for the subject-specific time series, as well as two control regressors to account for temporal fluctuations related to WM and CSF, respectively.

To assess group differences, higher-level FEAT analyses were carried for each seed using whole-brain mixed-effect analysis with FLAME 1+2 and a cluster-based threshold of $z > 3.1$, $p < 0.05$ FWE-corrected. The higher level GLMs included one regressor for the losartan group, one regressor for the placebo group and a control regressor containing structural grey matter maps to control for potential volumetric differences.

4.2.7. Statistical Analysis of Non-imaging Variables

Statistical analyses of non-imaging variables were carried out using SPSS software version 29 (IBM SPSS, Inc., Armonk NY), at an alpha-level of significance of 0.05. Any potential drug-induced changes in subjective mood and physiological parameters were assessed using 2x2 mixed model ANOVAs on VAS ratings and physiological parameters, with the between factor group (losartan, placebo) and the within factor time (pre and peak drug administration). A statistically non-significant group x condition interaction effect reflects no drug-induced changes.

4.3. Results

4.3.1. Group Matching and Drug Side Effects

An overview of participant characteristics including sociodemographic, clinical and personality measures is presented in Table 4.1. Acute administration of losartan had no effect on heart rate, blood pressure, or subjective state and mood ratings (Table 4.2). Furthermore, drug administration was not guessed above chance level by the experimenter or the participants (experimenter: 53% correct, p = .66; participants: 55% correct, p = .46)

Table 4.1. Participant Characteristics. Overview of sociodemographic measures as well as attentional, clinical and personality participant characteristics in the placebo and losartan group

	Placebo (N=24; 17 female)	Losartan (N=21; 16 female)
	M (SD)	M (SD)
Sociodemographic Measures		
Age	25.00 (6.71)	21.76 (2.99)
Years of education	17.17 (3.38)	17.00 (2.41)
Attentional, Clinical and Personality Measures		
ACS	48.75 (7.62)	49.51 (8.69)
BDI	10.29 (7.41)	9.24 (5.08)
BIS	12.13 (3.08)	12.19 (2.70)
BAS	25.04 (5.28)	25.00 (4.45)
ASI	33.75 (23.11)	28.71 (17.30)
STAI-T	49.83 (7.33)	46.84 (8.40)
EPQ – Psychosis	2.88 (1.89)	4.14 (4.93)
EPQ – Neuroticism	13.54 (4.98)	14.38 (6.10)
EPQ – Extraversion	10.17 (4.91)	14.24 (6.44)
EPQ – Lie	7.67 (3.68)	8.10 (3.38)

Note: ACS: Attentional Control Scale, BDI: Beck Depression Inventory, BIS: Behavioral Inhibition Scale, BAS: Behavioral Activation Scale, ASI: Anxiety

Sensitivity Index, STAI-T: Spielberger's Trait Anxiety Inventory, EPQ = Eysenck Personality Inventory

Table 4.2. Group Comparison of physiological measures and visual analogue scale (VAS) ratings before drug intake and at drug peak-level in the losartan vs placebo group. VAS ratings include subjective mood and state parameters. Heart rate is presented in bpm. Systolic and diastolic blood pressure are presented in in mmHg. p-values are based on the group x time interaction effect.

	Baseline		*Drug Peak Level*		
	Placebo M (SD)	Losartan M (SD)	Placebo M (SD)	Losartan M (SD)	p
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

4.3.2. ICA-Analysis

Decomposing spontaneous fluctuations of brain activity into resting state networks across groups. Out of the 25 ICA-identified group-averaged components, a total of 16 were defined as meaningful RSNs (Beckmann et al.,

2005; De Luca et al., 2006; Raichle et al., 2001; figure 4.1.). The remaining components reflected motion artefacts or BOLD signal drift-out and were therefore discarded. Table 4.3., contains the correlations between the identified components in this study and previously published RSN maps (Smith et al., 2009), which informed meaningful RSN selection. Due to the data-driven approach, ICA divided the DMN into two components, one component reflecting the entire DMN, and the second component consisting of the posterior DMN only. Similarly, the FPN was divided into the left FPN, right FPN and a prefrontal-executive network. In total, ICA analysis across groups, identified 6 RSNs of interest as justified above, including the SN (figure 4.1.-A), and 10 additional RSN components (figure 4.1.-B).

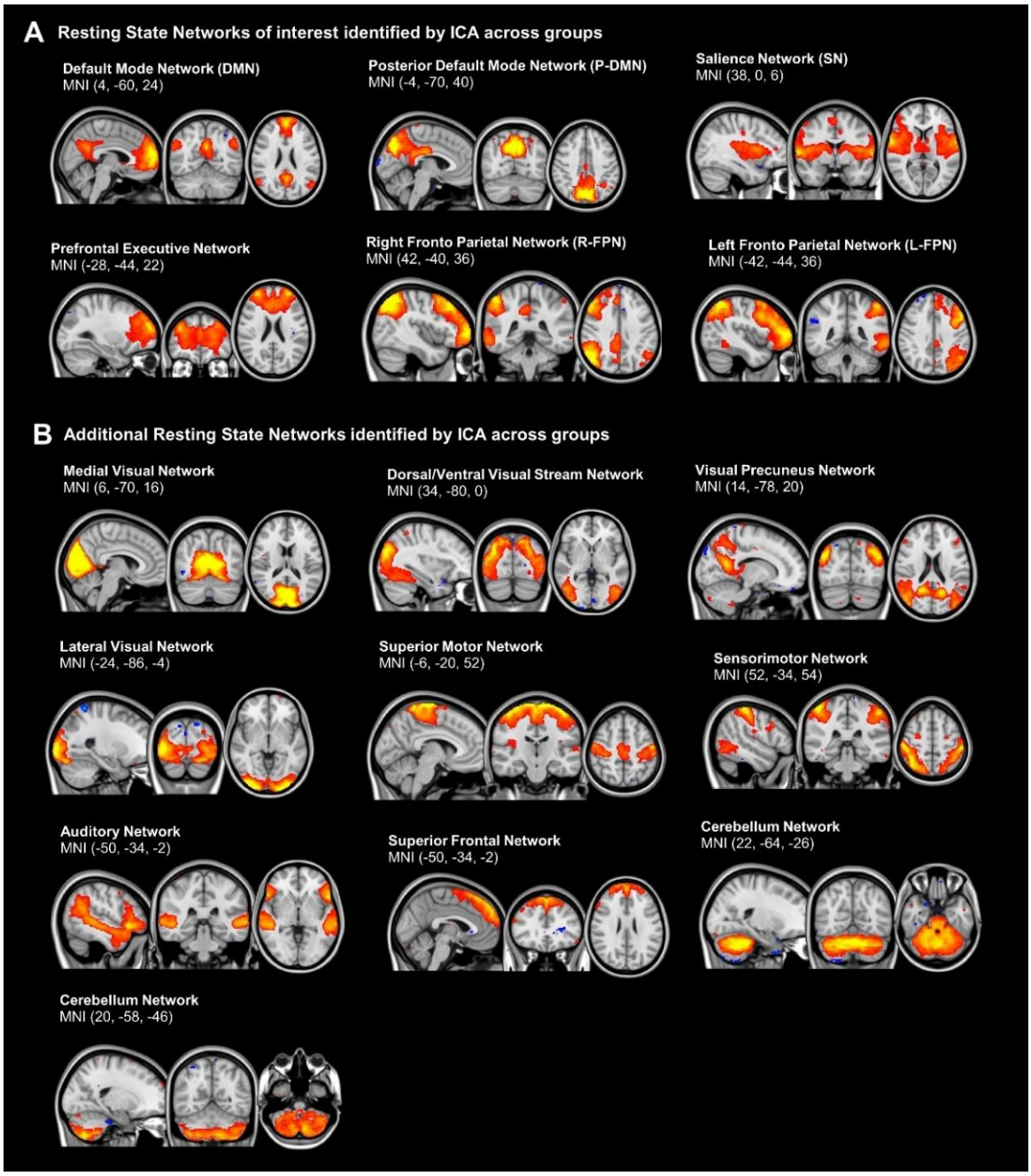


Figure 4.1. Group-Averaged Resting State Networks (RSN) identified by ICA. All images are thresholded at z > 3.1 **A:** Overview of the RSN of interest in this study, identified by ICA. Notably, ICA divided the DMN into two components. **B:** Additional RSN components identified by ICA, which are not central to the study.

Table 4.3. Correlations between RSNs in this study and previous published networks. Overall, most components align well between the visual inspection and the previously published components by Smith et al. 2009. Some components in this study, however, were not observed by the previously published components of Smith et al., hence the blank spaces in the table. The column 'component Nr' corresponds to the numeric classification of each component by the ICA output, prior to being identified as a meaningful network and label accordingly through visual inspection. Notably, what was identified as the 'salience network' (SN) via visual inspection correlates highly with the 'auditory network' by Smith et al. Our choices on identifying this component as the SN was informed by the presence of the insula in this component, while the second RSN correlating with Smith et al.'s 'auditory network' does not include the insula. The RSNs by Smith et al., do not include the SN.

Component	Comp Nr	Smith label	r
Components of interest			
DMN	1	DMN	.51
Posterior DMN	10	DMN	.47
SN	2	auditory	.64
Prefrontal Executive Network	11	Executive Network	.61
R-FPN	4	R-FPN	.62
L-FPN	6	L-FPN	.70
Additional components			
Medial Visual Network	0	Medial Visual	.76
Dorsal/Ventral Visual Stream Network	3	Lateral Visual	.67
Visual Precuneus Network	13	DMN	.31
Lateral Visual Network	20	visual	.61
Superior Motor Network	7	Sensorimotor	.35
Sensorimotor Network	-	-	-
Auditory Network	17	auditory	.42
Superior frontal Network	-	-	-
Cerebellum Network I	14	cerebellum	.57
Cerebellum Network II	-	-	-

Note. DMN: Default Mode Network, SN: Salience Network, R/L-FPN: Right/Left Fronto-Parietal Network

4.3.3. Independent Component Analysis

Contrary to our expectation, the ICA-based analysis showed no ARB drug effects in any RSN. For descriptive purposes, peak voxel information and p-values for the networks of interest (DMN, posterior DMN, SN, prefrontal executive network, R-FPN, L-FPN) are presented in table 4.4.

Table 4.4. Peak voxel information of ICA results for each meaningful Resting State Network (RSN). The MNI column represents peak voxel coordinates, corr-p corresponds to the threshold-free-cluster-enhancement (tfce) corrected p-value of the peak voxel. Location refers to the corresponding brain region of the peak voxel.

RSN	MNI	corr-p	Location
Placebo > Losartan			
DMN	[-56, -40, 35]	.783	Middle temporal gyrus
Posterior DMN	[60, -62, 8]	.988	Lateral occipital cortex
SN	[30, -72, -2]	.409	Occipital fusiform gyrus
Prefrontal executive network	[48, -60, 24]	.244	Lateral occipital cortex
R-FPN	[-32, 10, 30]	.701	Middle frontal gyrus
L-FPN	[60, -48, 8]	.755	Middle temporal gyrus
Losartan > Placebo			
DMN	[-26, -34, -28]	.256	Posterior fusiform gyrus
Posterior DMN	[-10, 0, 68]	.204	Superior frontal gyrus
SN	[40, -88, -4]	.376	Lateral occipital cortex
Prefrontal executive network	[8, -16, 15]	.587	Precentral gyrus
R-FPN	[4, 16, 62]	.119	Superior frontal gyrus
L-FPN	[-42, -12, -16]	.662	White matter

Note DMN: Default Mode Network, SN: Salience Network, R/L-FPN: Right/Left Fronto-Parietal Network

4.3.4. Seed-based Analysis

Compared to placebo, losartan administration had no effect on rsFC in the fear network seeds (amygdala, anterior insula) but modulated rsFC of the memory network seeds (hippocampus, posterior PHC). Specifically, losartan reduced rsFC between the hippocampus and the inferior frontal gyrus (IFG;

MNI peak-voxel coordinates: x = 62, y = 18, z = 24; figure 4.2.-A). With regards to the PHC seeds, losartan reduced rsFC between the posterior PHC and three clusters within the dlPFC, particularly localised in the left DLPFC (1 cluster; MNI peak-voxel coordinates: x= -30, y = 42, z = 36; figure 4.2-B) and right DLPFC (2 clusters; MNI peak-voxel coordinate cluster 1: x = 28, y = 38, z = 34; cluster 2: x = 26, y = 40, z = 48; figure 4.2.-B). There were no drug-induced rsFC changes linked to the anterior PHC seed. Exploratory analyses on the vmPFC seed did not show any losartan-induced effects.

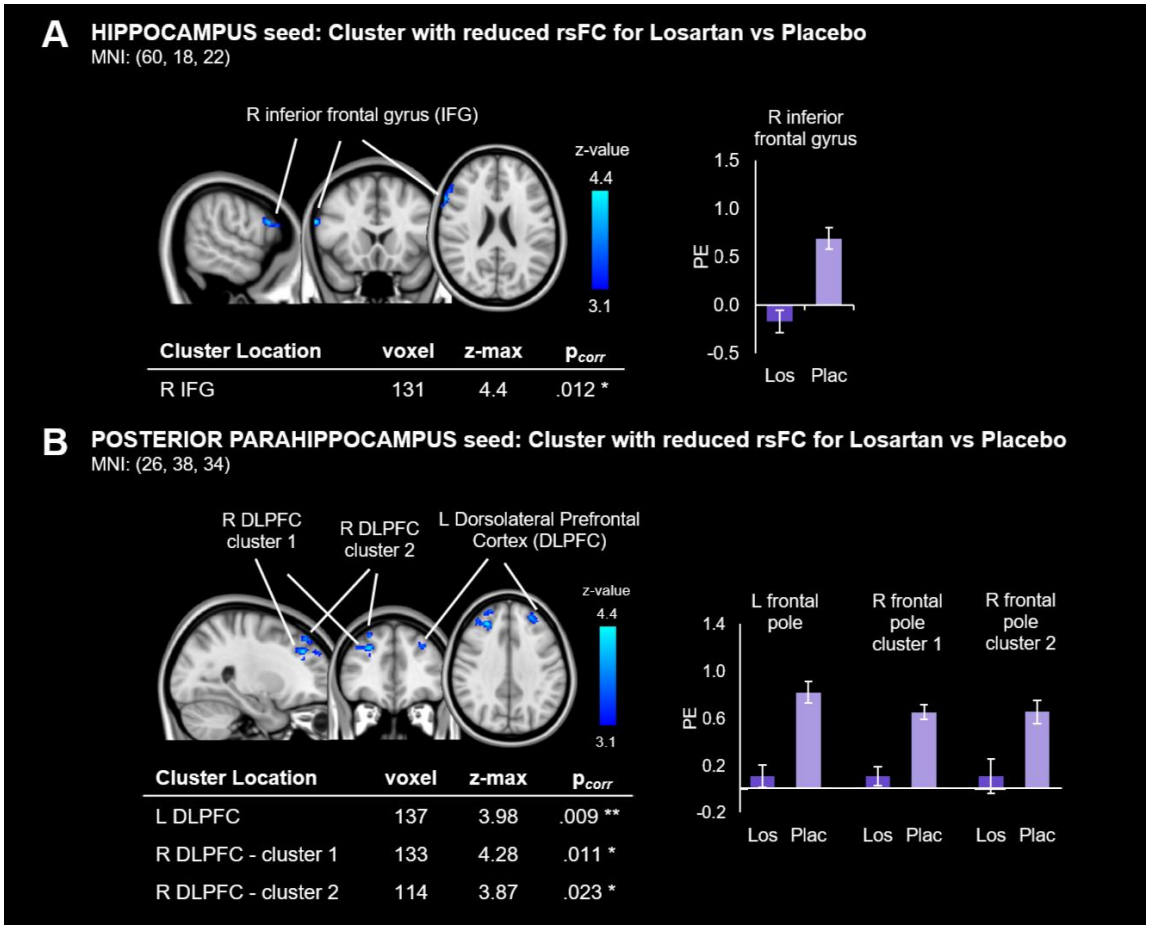


Figure 4.2. Seed-Based Resting State Functional Connectivity (rsFC) Results. Statistics are based on z > 3.1, p < 0.05, family-wise-error (FWE) corrected; the tables below the brain images show additional cluster information. **A:** Compared to placebo, losartan reduced rsFC between the hippocampus and inferior frontal gyrus (IFG). The extracted parameter estimates are presented to the right. **B:** Compared to placebo, losartan reduced rsFC between the posterior parahippocampus and three clusters within the dorsolateral prefrontal cortex (DLPFC). The extracted parameter estimates are presented to the right. *p<.05; ** p<.01.

4.4. Discussion

This study aimed to investigate potential modulatory effects of ARBs on the intrinsic organization of the brain reflected by rsFC, particularly focusing on PTSD associated networks. Data-driven ICA revealed no ARB effects within the derived RSNs. Seed-based analyses suggested that a single dose of losartan decreased rsFC between the memory network seeds and frontal cortex, specifically (i) between the hippocampus and the IFG (ii) and between the posterior PHC and the DLPFC. In contrast, ARB administration did not show a modulatory role on the fear network seeds, as indicated by the lack of ARB effects on the amygdala and anterior insula seed.

To explore the intricate impact of central ARB action, rsFC offers a more in-depth examination of how ARBs modulate the functional significance of brain structures beyond their cognitive engagement in task-based studies. While in task-based studies modulatory effects of ARB on the fear network and memory network have been observed (Reinecke et al., 2018; Shkreli et al., 2024; Xu et al., 2022), our results suggest that acute ARB administration affects the internal organisation of structures within the memory network rather than within the fear network.

Traditionally, ARB research has primarily focused on the fear network, due to their proposed role in preventing PTSD symptoms (Khoury et al., 2012; Seligowski et al., 2021) and their anxiolytic effects in animal studies (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012). However, there is increasing evidence that the extended memory network, including higher-order visual processing areas like the PHC or lingual gyrus, play a yet underestimated role in PTSD psychopathology (for reviews, see Fleming et al., 2024; Joshi et al., 2020) and central ARB action (Bild et al., 2013; Fogari et al., 2003; Fogari et al., 2006; Salmani et al., 2020; Shkreli et al., 2024; Shkreli et al., 2020). Our results align with this emerging perspective underscoring the complexity of neural ARB modulation, and the importance of

considering broader neurocognitive mechanisms in understanding the impact of ARBs on PTSD psychopathology.

4.4.1. Decreased Coupling between Hippocampus and IFG

More specifically, our results show an ARB-induced decrease in rsFC between the hippocampus and the IFG, which is part of the SN (Seeley et al., 2007). The IFG has been implicated in a variety of cognitive processes at the intersection of attention, emotion and episodic memory (Cha et al., 2016; Greenberg et al., 2005; Hampshire et al., 2010), and there is emerging evidence suggesting its relevance in threat processing (Mujica-Parodi et al., 2017; Pfeuty et al., 2015; Rahko et al., 2010), and aversive memories (Battaglini et al., 2016; Bourne et al., 2013; Clark et al., 2016; Kelly et al., 2007). Since our results show that ARBs reduced rsFC between the IFG and the hippocampus, this may reflect a disengagement of stimuli eliciting a SN response from their facilitated memory mechanism, i.e. ARBs may reduce the influence of emotional valence on memory formation. This is in line, with previous findings showing that ARBs reduced learning from aversive compared to appetitive outcomes (Pulcu et al., 2019) and reduced memory advantages of negative images (Xu et al., 2022). Notably, while it has been shown that during memory encoding of negative images losartan reduced task-based hippocampus – amygdala coupling (Xu et al., 2022), our results further expand on these findings, suggesting that a decreased coupling between the hippocampus and the SN may already manifest at rest.

With regards to PTSD, such decreased coupling between the hippocampus and IFG would imply that traumatic stimuli, or the distress associated with traumatic stimuli, undergo a less pronounced integration into autobiographical memory. Interestingly, it has been shown that PTSD patients had greater hippocampus – IFG connectivity compared to trauma exposed controls in resting state studies (Sheynin et al., 2020), while 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). Thus, our results may imply that ARBs may modulate the development of memory intrusions by reducing hippocampus – IFG coupling. Notably, such increased IFG activation in task-based studies was shown during memory encoding for distressing scenes and images which later manifest as involuntary memories (i.e. 'intrusive scenes/images') and during involuntary memory recall of traumatic scenes (Clark et al., 2016). Thus, it has been argued that IFG activation during memory encoding imprints a neural signature to the content becoming an intrusive memory, while IFG activation during involuntary memory retrieval prompts an attentional redirection towards the intrusive memory via reinstating the established 'neural signature' (Clark et al., 2016). This highlights that intrusive memory encoding and retrieval are highly interconnected, which was evidenced by insights from fundamental neurocognitive research showing that the neural pattern during memory encoding can predict what information will be remembered or forgotten ('subsequent-memory effect') (Clark et al., 2016). Thus, the present ARB-induced reduction in hippocampus-IFG rsFC may be associated with both – an ARB-induced reduction in encoding of intrusive scenes or an ARB induced reduction in recall of intrusive memories, particularly given that the hippocampus is not only relevant for memory encoding but also memory recall. However, this interpretation that ARBs may modulate memory intrusion development remains speculative and needs detailed investigation in future research.

4.4.2. Decreased Coupling between PHC and DLPFC

The current results further show an ARB-induced decrease in rsFC between the posterior PHC seed and DLPFC, which is part of the FPN (Seeley et al., 2007). The FPN is involved in top-down executive control, working memory and goal-directed behaviour (Seeley et al., 2007), so that an ARB-induced

decrease in rsFC with the PHC may imply a decreased coupling between executive control mechanisms and higher-order visual processing.

This result may be counterintuitive from a memory network perspective as the FPN, and in particular DLPFC involvement, has been associated with improved memory formation (Leshikar et al., 2017; Sandrini et al., 2014; Summerfield, Greene, et al., 2006). However, such studies primarily investigated DLPFC activity, DLPFC stimulation, or DLPFC connectivity during task-based memory encoding (Sandrini et al., 2014; Summerfield, Greene, et al., 2006), making direct comparisons to the present findings on functional connectivity at rest difficult.

It has been discussed that during memory formation the PFC is involved in selectively prioritising visual information via top-down control (Blumenfeld & Ranganath, 2007; Paneri & Gregoriou, 2017; Summerfield, Greene, et al., 2006). Thus, our findings may suggest that ARB administration reduced coupling of visual-memory processes in the PHC from top-down executive control mechanisms through the DLPFC. Speculatively, reduced top-down control from the DLPFC on perceptual information processed by PHC could potentially preserve the perceptual richness of a complex scene, which may enhance the perceptual integration of complex scenes into episodic memory and/or facilitate the integration of objects into spatial contexts. Particularly, given that ARBs have also been shown to enhance PHC activity and stability during memory encoding as shown in chapter 2 and chapter 3, alongside facilitating visual processing (Shkreli et al., 2020). Taken together, such decreased rsFC coupling from executive control structures might also be cautiously interpreted as facilitated PHC processing. Alternatively, since the DLPFC is primarily involved in working memory (Barbey et al., 2013) and the PHC is involved in spatial binding of visual working memory (Luck et al., 2010; Schon et al., 2016), a decreased coupling may imply an ARB effect on working memory rather than episodic memory.

Notably, PTSD-related alterations in PHC and DLPFC activity have been repeatedly reported in task-based fMRI studies (for meta-analytic review see Kunimatsu et al., 2020). Also, there is preliminary evidence of higher PHC – DLPFC connectivity being associated with greater PTSD symptom severity in a task-based functional connectivity study in assault-exposed (vs non-exposed) adolescent girls (Cisler et al., 2013). However, direct rsFC effects between PHC and DLPFC have not been reported yet. Taken together, it seems that PHC – DLPFC connectivity might be relevant in PTSD psychopathology, but their distinct behavioural or psychopathological manifestation is not understood yet. The present findings point towards a potential reduction in this connectivity via ARB administration, but further research is warranted to understand the full spectrum of implications.

To complement the seed analyses, we included a data-driven approach using ICA. However, we found no ARB effects in any of the identified RSNs. Potentially, ARB rsFC effects are subtle and localized to specific brain structures. In this case, ICA may be less sensitive to detect such effects compared to seed-based analyses.

4.4.3. Limitations and Further Directions

This study has some limitations. First, our sample consists of healthy volunteers. Although we recruited high trait anxious participants as a first step towards a more clinically relevant approach, the results cannot be translated into a clinical PTSD population. Thus, next steps would include to translate these findings 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 the clinical use of ARBs in PTSD and other psychiatric disease. For instance, although there are common rsFC changes associated with PTSD, the exact pattern of rsFC manifestations has been shown to depend on specific symptom clusters

(Lebois et al., 2022; Tursich et al., 2015) and might differ between sexes (Helpman et al., 2021). Thus, subtle ARB effects on rsFC might be overshadowed by sub-group variations within a psychiatric disease, making their clinical translation more challenging.

In conclusion, the current study opens a new pathway for investigating neurobiological dynamics of central ARB action via rsFC. Our results suggest that ARBs exert localized effects on rsFC by decreasing the functional coupling of the structures within the memory network (hippocampus, PHC) from modulating structures outside the memory network, in particular the SN and the FPN. With regards to PTSD, such decreased coupling with the SN may particularly imply that functional memory formation is preserved. Although ARBs did not affect the fear network seeds, our results show that ARBs might play a role in the intersection between emotional processing and memory formation via decreased hippocampus – IFG connectivity. Moving forward, it is important to understand how these observed rsFC effects manifest in behavioural correlates and clinical outcomes to unravel potential implications of ARBs in PTSD psychopathology.

5

Chapter 5
The effect of ARBs on the Stress Response

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Key abbreviations

CBG: Corticosteroid-Binding-Globulin

CRF/CRH: Corticotrophin Releasing Factor/Hormone

HR: Heart Rate

HRV: Heart Rate Variability

HPA (axis): Hypothalamic-Pituitary-Adrenal

SNS: Sympathetic Nervous System

The effect of ARBs on the Stress Response

Moving beyond the neural actions of ARBs, the last data chapter investigates their role in modulating the stress response. Focusing on markers of subjective stress, SNS activity and HPA axis response, this chapter examines questionnaire data, HR/HRV and salivary cortisol levels in response to acute ARB administration versus placebo. In addition, an exploratory analysis on potential interaction effects between ARBs with hormonal contraceptives was included, given that the cortisol stress response is modulated by hormonal contraceptive intake.

5.1. Introduction

The Renin-Angiotensin-System (RAS), which is involved in regulating vascular constriction and blood pressure (Peach, 1977), has been increasingly implicated in psychopathology – most notably in anxiety and posttraumatic stress disorder (PTSD). In particular, angiotensin-II receptor blockers (ARBs) had direct anxiolytic effects in rodent models (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012), while being associated with reduced PTSD symptom development in human population-based studies (Khoury et al., 2012; Seligowski et al., 2021). Yet, the underlying mechanisms remain to be understood.

Angiotensin-II receptors are widely expressed throughout the brain, including core regions in which fear-related structural and functional aberrations have been observed – such as the amygdala and hippocampus (von Bohlen und Halbach & Albrecht, 2006). Thus, previous research has primarily focused on investigating emotional processing, and more recently memory formation as highlighted in the previous chapters, to elucidate the underlying mechanisms in psychopathology. As a result, it could be demonstrated that ARBs modulate a variety of neurocognitive domains,

such as reward learning (Pulcu et al., 2019; Zhou et al., 2023), threat processing (Reinecke et al., 2018), (emotional) memory formation (Xu et al., 2022), visual processing (Shkreli et al., 2020), and fear learning (Zhang et al., 2023; Zhou et al., 2019).

An essential yet underexplored aspect linking RAS activity to neurocognitive functioning and psychopathology involves its role in modulating the stress response. For instance, in rodent studies and in-vitro models it was shown that angiotensin-II stimulates sympathetic nervous system (SNS) activity through reinforcing noradrenaline release (Brasch et al., 1993; Campese et al., 2005; Dendorfer et al., 2002; Gironacci et al., 1994), as well as stimulating the hypothalamic-pituitary-adrenal (HPA) axis through reinforcing corticotropin releasing factor (CRF; in humans corticotropin releasing hormone - CRH) (Sumitomo et al., 1991) and ACTH (Adrenocorticotropic hormone) release (Sobel & Vagnucci, 1982; Spinedi & Negro-Vilar, 1983). Notably, the HPA axis is the core bodily stress system, in which CRF/CRH release marks the onset of an enzyme cascade, including ACTH release and resulting in the synthesis of cortisol, which is one of the most extensively studied endocrine markers in stress research in general – and in PTSD in particular (Lehrner et al., 2016).

The endocrine stress response includes various catecholamines (e.g. noradrenaline), neuropeptides (e.g. CRH/CRF) as well as corticosteroids (e.g. cortisol). It is their balanced interplay which ensures adaptive behavioural and neurocognitive reactions to moderate stress (for review, see Schwabe et al., 2022). For instance, during stress exposure joint glucocorticoid and catecholamine actions prompt a shift towards associative stimulus-response learning based on amygdala-striatum activity. However, while this enables a rapid adaption to stress, it compromises hippocampus-dependent cognitive and contextual learning, which is important for an accurate integration of experiences into the episodic memory system (de Quervain et al., 2017; Schwabe et al., 2022). Thus, disturbances between these systems may

increase the risk of psychopathology, for instance caused through *extreme* stress exposure during traumatic experiences (Goodman et al., 2012). In this regard, prominent PTSD theories suggest that traumatic experiences exaggerate associative learning between low-level perceptual features and fear over adaptive memory formation (Goodman et al., 2012; Pitman et al., 2012). As a result, this may prompt a dysfunctional integration of traumatic events into the episodic memory system, in which perceptually similar cues can trigger re-experiencing symptoms (Berntsen, 2009; Brewin, 2014; Brewin et al., 1996; Ehlers & Clark, 2000; Goodman et al., 2012). From an endocrine perspective, this is in line with previous research showing that cortisol modulates memory formation resembling an inverted U-function, in which extremely elevated and attenuated cortisol levels were associated with memory impairments (de Quervain et al., 2017). Similarly, amygdala function has been enhanced through glucocorticoid and noradrenaline modulation (Schwabe et al., 2022).

Taken together, extreme stress during trauma exposure interferes with adaptive neurocognitive processing (Berntsen, 2009; Brewin, 2014; Brewin et al., 1996; Ehlers & Clark, 2000), potentially reinforced by angiotensin-II action shown to stimulate the HPA axis (Aguilera et al., 1995; Müller et al., 2007; Sumitomo et al., 1991). Thus, ARBs may exert their suggested protective effects on PTSD development by directly mitigating the endocrine stress response at trauma exposure. In turn, this may preserve more adaptive neurocognitive processing and a functional integration of the traumatic experience into the episodic memory system. This highlights that investigating the endocrine stress response might be one of the missing links in current research of central ARB action and neurocognitive processing.

There is initial evidence from animal studies showing promising results, in which ARBs downregulated HPA-axis response via preventing stress-induced changes in CRF receptor binding (Pavel et al., 2008) and reducing corticosterone secretion, which is the animal analogue to cortisol (Armando

et al., 2001). Similarly, after ARB administration, the SNS stress response was attenuated (Pavel et al., 2008). However, despite the crucial role of stress in PTSD development and ARB effects in the rodent stress response, there are only limited investigations in humans. So far, it has been shown that during exposure to distressing film material as a trauma-analogue experience, an acute dose of the ARB losartan prevented an increase of the physiological stress response and SNS activity (Shkreli et al., 2020). This was reflected by a lower heart rate (HR) and a reduced low-frequency to high-frequency (LF/HF) ratio of heart rate variability (HRV) (Shkreli et al., 2020). However, no study has probed the effects of ARBs on cortisol or HPA axis activity, despite cortisol being implicated in PTSD development. Further, no study has investigated if ARB effects are limited to anxiety and fear-related traumatic stress or whether they extend to the general stress response more broadly.

The study presented in this chapter takes a first step to investigate whether ARBs modulate the HPA axis stress response reflected by salivary cortisol levels during a performance stress paradigm (Wright et al.). Further, we aim to replicate and extend previous findings on losartan and physiological stress and SNS activity (Shkreli et al., 2020) by including measures of HR and the LF/HF ratio of HRV (Rajendra Acharya et al., 2006). We hypothesize that a single dose of losartan compared to placebo (i) reduces subjective stress reflected by lower stress and anxiety ratings on self-reported questionnaires administered immediately after the stress paradigm, (ii) reduces the physiological and SNS stress responses reflected by lower HR and lower LF/HF ratio during the stress paradigm, and (iii) reduces HPA axis activity reflected by lower salivary cortisol levels in response to the stress paradigm.

Notably, examining the impact of ARBs on the cortisol response may require considering modulatory effects of oestrogen on the cortisol response (Jentsch et al., 2022). Critically, oestrogen levels can be modulated by hormonal contraceptives in humans. In this regard, it has been shown that

hormonal contraception users exhibit higher basal cortisol levels but a blunted cortisol response to acute stress (Gervasio et al., 2022; Hertel et al., 2017; Jentsch et al., 2022). Thus, endocrine studies on cortisol commonly exclude hormonal contraceptive users to account for this confounding factor. However, in the current study their inclusion presents a valuable opportunity to examine whether ARB action is influenced by hormonal contraception. Particularly, preliminary evidence in rodent models suggest a modulatory role of oestrogen in RAS activity and ARB response (Hajmohammadi et al., 2019; Miller et al., 2006; O'Hagan et al., 2012; Parrish et al., 2019), emphasizing the need for human translation. Thus, we included exploratory analyses on potential interaction effects between ARBs and hormonal contraception.

5.2. Methods and Materials

5.2.1. Participants

60 healthy participants (aged 18 – 34) were recruited for this study. The inclusion criteria consisted of being aged 18-50, BMI of 18-30, not pregnant/breastfeeding, smoking <5 cigarettes/day, not taking any CNS active medication in the past 6 weeks, not taking any blood pressure medication or aliskiren, not having poor oral health (such as bleeding gums), not taking any steroid medication, not diagnosed with a serious medical condition, no personal or family history of a severe psychiatric condition. Further, participants had to refrain from strenuous exercise for 24 hours and from food for one hour prior to testing, to not confound salivary cortisol assessments.

To characterize the sample, the study assessed demographic information and several baseline questionnaires: STAI-T (Spielberger et al., 1970), Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975), Anxiety

Sensitivity Inventory (Taylor & Cox, 1998), Beck Depression Inventory-II (Beck et al., 1996), Attention Control Scale (Derryberry & Reed, 2002), Behavioural Inhibition and Activation Scale (Carver & White, 1994). All participants gave written informed consent. The study was approved by the University of Oxford Medical Sciences Research Ethics Committee (ethics reference R65978/RE003).

5.2.2. Stress Manipulation - The Oxford Cognition Stress Test (OCST)

The OCST is a newly developed computerised paradigm to induce performance stress (Wright et al.). During an introductory video, participants are deceived to believe that the paradigm measures cognitive ability across three different domains (see figure 5.1.-A), in which they would be compared to the general population. Through standardised introductory questions (e.g. on their highest degree) and easy practice runs, participants are made to believe that task difficulty is tailored to their individual profile, and that they should expect to score 70-90% accuracy. In addition, they are told to receive feedback on their individual strengths and weaknesses in their cognitive abilities. However, the task is designed to induce high failure rates. An algorithm controls task difficulty and response time windows, to ensure that participants score less than 50% correct within each domain. While engaged with the task, participants continuously hear a ticking clock and are presented with a colour bar indicating their task performance from green (well above fictitious average) to red (well below fictitious average). On incorrect trials they receive negative feedback via an angry face, verbal prompt ('WRONG! Please try harder') and aversive sound. At the end of completing each domain, participants receive their 'results', which consist of a fictious distribution on general population performance, in which their score is placed below average (see, figure 5.1.-B). To further increase social pressure, the experimenter stays in the room throughout the task, although

they do not interact with the participant. The experimenter gives short and evasive answers to potential questions.

The three domains consist of the following:

Mental Arithmetic. Mental arithmetic tests were performed across three blocks of approximately 3 min each. In the first block, participants received easy equations, which increased in their difficulty level if participants achieved high accuracy scores (e.g. level 1: 5+3; level 4: (4 x 9) - 10 + 19). In addition, the response time window decreased at higher accuracy scores. Participants were not told their difficulty level, and the new block starts at the difficulty level of the previous block.

Verbal Intelligence – Anagrams. Participants were made to believe that this task measures their verbal intelligence. They were presented with a jumbled letter string to rearrange in a way that results in a meaningful English word. All participants were presented with one block of the same 11 anagrams, in which some were impossible to solve. They had 30 seconds to complete each anagram.

Attention – Visual Search. Participants were engaged with one block of approximately 5 minutes. They were instructed to locate the target 'blue T' via mouse click on the screen, while the screen was filled with distractors consisting of green L, blue L and green T stimuli. In case participants achieved high accuracy scores, difficulty level (reflected by the number of distractors) increased while the response time window decreased.

All participants were presented with the same order: Mental Arithmetic 1 – Anagrams – Mental Arithmetic 2 – Visual Search – Mental Arithmetic 3 (figure 5.1.-C).

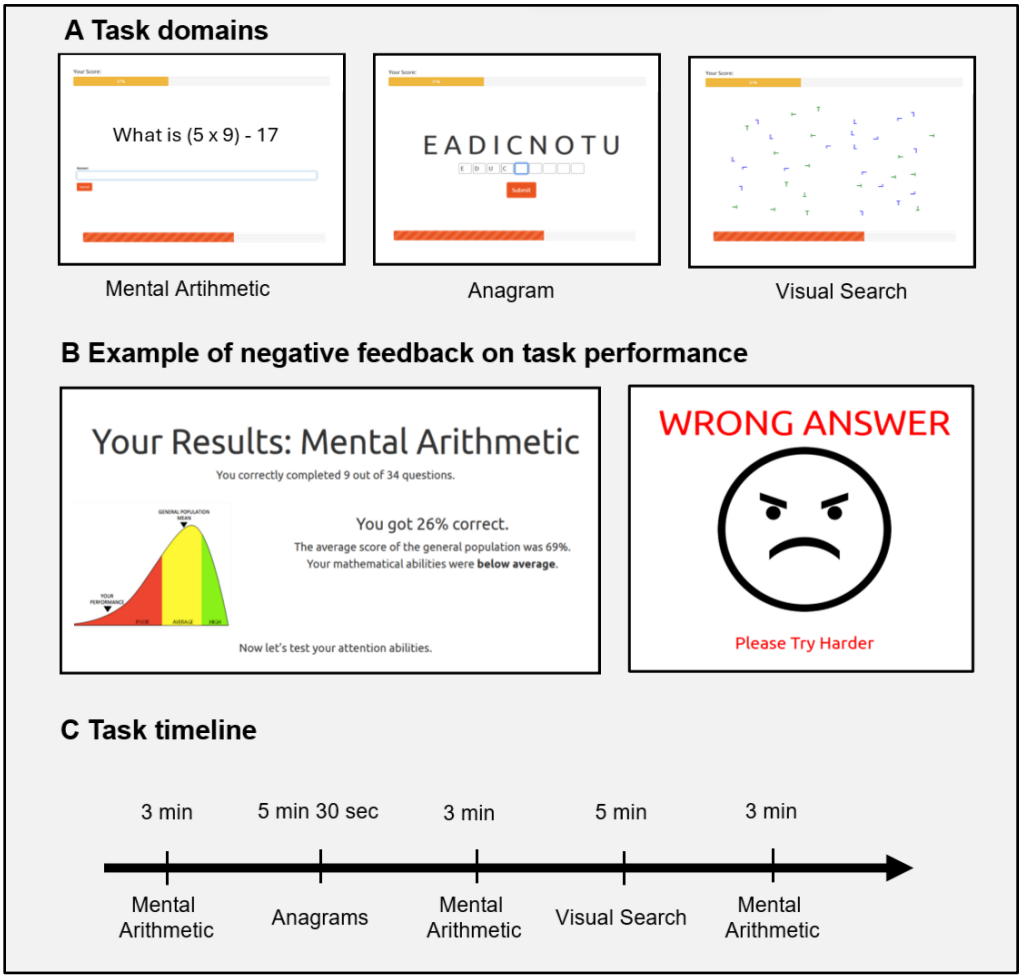


Figure 5.1. Overview of the Oxford Cognition Stress task (OCST). A: The three task domains consist of mental arithmetic, anagrams, and visual search parts. A bar at the top of the screen indicates correct task performance, while the bar the at the bottom of the screen keeps track of the time limit. B: Participants are presented with the incorrect feedback that their task performance is below average compared to the general population (left). During the task, in case participants made a mistake, they receive harsh negative feedback (right). C: Timeline of the task, which is the same for all participants.

5.2.3. Stress Response Measures

Subjective Stress Response. Subjective stress was measured via the STAI-S (Spielberger et al., 1970) and a VAS rating on the item 'stressed' (range 0 – 100). To prevent response bias, the VAS item 'stressed' was embedded within 13 VAS items assessing mood and physiological state (e.g. 'sad', 'alert', 'dizzy')

ensuring that participants did not guess the stress inducing purpose of the OCST.

Heart Rate and Heart Rate Variability. HR and HRV were based on R-to-R interval data, measured via short-range telemetry (POLAR RS800CX). R-to-R interval data was pre-processed and analysed using Kubios HRV Scientific Lite Software. As recommended, preprocessing steps included inter-beat-interval detrending via the 'smoothing priors' approach with a cut-off frequency of 0.035 Hz (Tarvainen et al., 2002), and artefact beat correction with a medium threshold of 0.25 seconds (Tarvainen et al., 2021; Tarvainen et al., 2014). For statistical analyses of HRV data, the low-frequency/high-frequency (LF/HF) ratio was used, which was based on frequency-domain results via Fast Fourier Transformation (Tarvainen et al., 2014).

Salivary Cortisol. Salivary cortisol was assessed via Salivettes (Sarstedt). Participants were instructed to gently chew on the cotton bud of the Salivette for one minute. To remove human tissue Salivettes were centrifuged for 2min on 1000g, then aliquoted to 2ml Eppendorf tubes, prior to being freezed on -20 °C. Cortisol samples were sent for laboratory analyses to the Department of Biological Psychology at Technische Universität Dresden, Germany, under the lead of Prof Clemens Kirschbaum. As recommended in dealing with outlier values in hormonal research (Herbers et al., 2021), a fixed value imputation was conducted on outlier data (+/- 3 SDs) with the highest non-outlier value per assessment point (pre-stress: 1 value (1.85 %), peak-stress: 2 values (3.70 %), 20min post stress: 2 values (3.70 %), 40 min post-stress: 1 values (1.85 %)). As a measure of cortisol stress response, the area under the curve (AUC) with respect to ground (AUCg) and the AUC with respect to increase (AUCi) were calculated (Pruessner et al., 2003).

AUCg is a measure of total cortisol levels which is calculated based on the amount of cortisol at the initial measurement (pre-stress), as well as the change between each measurement. On the other hand, AUCi focuses solely

on the changes between cortisol measurement over time and does not consider how high cortisol levels were at the initial pre-stress assessment (see figure 5.2.).

To improve skewness and normality cortisol levels were log-transformed prior to statistical analysis. AUCg and AUCi were calculated prior to being log-transformed to preserve their interpretability.

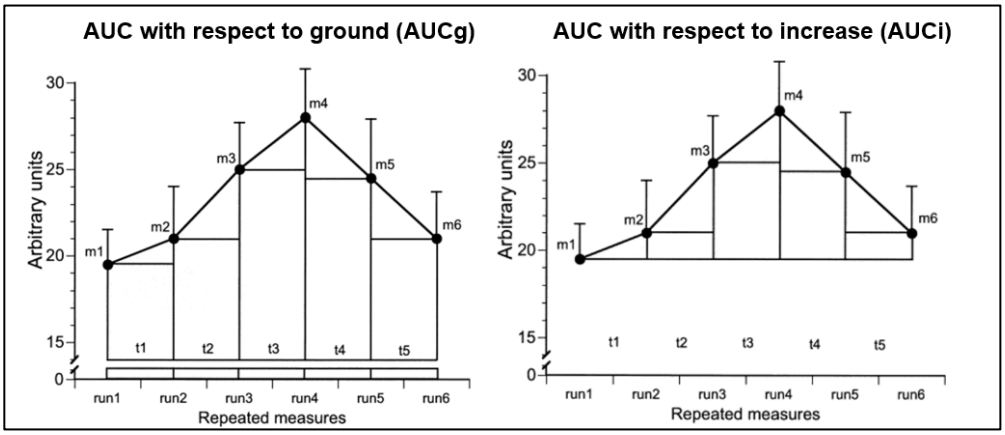


Figure 5.2. Overview of Area Under the Curve (AUC) measures. Figure reproduced from Pruessner et al. 2003 - pp. 918/920. This figure illustrates how the two different AUC parameters are calculated. The AUCg includes basal cortisol levels in addition to cortisol changes between measurement points (m1 to m6) over time (t1 to t5), as reflected by the area for AUCg calculation starting from 0 on the y-axis. On the other hand, the calculation of AUCi only considers the changes in cortisol levels between measurements (m1 to m6) over time (t1 to t5), as reflected by the area for AUCi calculation starting at ~20 on the y-axis in this example. While m1 to m6 reflect cortisol levels, t1 to t5 reflect the time interval between measurement points.

5.2.4. Procedure

After online screening to assess eligibility, participants were invited to an in-person testing session. An independent researcher randomly allocated participants to either receive 50mg losartan (Cozaar; Merck Sharp & Dohme Ltd) or matched placebo (microcrystalline cellulose; Rayotabs, Rayonex GmbH) stratified for gender via a blocked randomisation sequence (blocks of four) created by a random number generator (random.org). The losartan dose was based on previous research (e.g. Pulcu et al., 2019; Reinecke et al.,

2018; Shkreli et al., 2020) showing that it is well tolerated and effectively modulates neurocognitive processing while not affecting physiological parameters such as blood pressure and heart rate. Losartan and placebo pills were over-encapsuled by an independent researcher to look identical and handed to the experimenter on the day before the testing session in an envelope labelled with the participant ID.

The testing session commenced between 12pm and 1pm to account for diurnal fluctuations on cortisol response (Adam et al., 2017),. Upon arrival on the testing day, eligibility was confirmed, and participants completed the baseline questionnaires and provided the first salivary cortisol sample to ensure there were no differences in cortisol levels prior to drug administration. To ensure that drug administration did not induce response bias, HR, blood pressure and VAS ratings on subjective mood and state, were assessed prior to drug administration and at drug peak level (1 hr; Lo et al., 1995; Ohtawa et al., 1993).

The stress manipulation commenced after drug peak levels were reached. It consisted of a pre-stress assessment, the OCST taking ~20 min, post-stress assessment, 20min post-stress assessment and 40min post-stress assessment. The pre-stress assessment included the second salivary cortisol sample, subjective stress measures (VAS rating, STAI-S) and baseline HR (measured continuously for 2min). While participants completed the OCST, HR was continuously measured. The peak stress assessment, immediately after the OCST, included the third salivary cortisol sample and subjective stress measures (VAS rating, STAI-S). To assess stress recovery, the 20min post-stress and 40min post-stress assessments included the fourth and fifth salivary cortisol sample as well as subjective VAS ratings, respectively. For an overview, see figure 5.3.

Subsequently, participants were asked to indicate whether they guessed the stress deception, and they were debriefed about the purpose of the task. In

the end, participant and experimenter guessed drug group allocation as a measure of whether double-blindness was preserved.

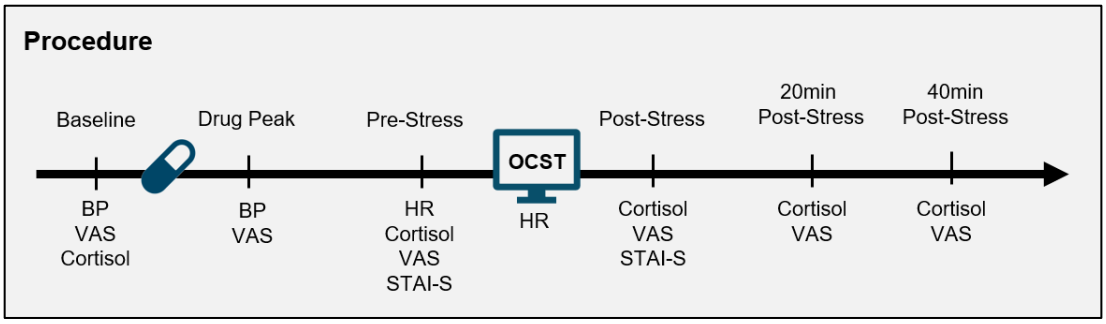


Figure 5.3. Procedure of the testing day. The upper part of the timeline represents the assessments, while the lower part contains the measures. BP = Blood Pressure, VAS = Visual Analogue Scale, HR = Heart Rate, STAI-S = Spielberger's State Anxiety Scale, OCST = Oxford cognition stress task.

5.2.5. Statistical analyses

Data analysis was conducted using R Software version 4.2.1.

To ensure that there were no drug-induced changes in physiological parameters or subjective VAS ratings, we used mixed model ANOVAS with the within factor time (pre drug administration, peak drug administration) and the between factor group (losartan, placebo). A statistically non-significant time x group interaction effects reflects no drug-induced changes.

To investigate OCST task performance, mixed-model repeated measure ANOVAs were used for the mental arithmetic task with the within factor block (block 1, 2, 3) and the between factor group (losartan, placebo). Performance on the anagram task and visual search task was analysed using two-sided independent samples t-test. Statistical tests on group differences in these measures were included as a manipulation check to ensure that any potential drug effects on the stress response were not biased by differences in task performance (e.g. one group performing better than the other, and

thus perceiving the task less stressful) or differences in correctly guessing the stress deception.

We investigated changes in subjective stress response (STAI-S and VAS rating), HR and HRV using mixed-model repeated measure ANOVAs with the within factor time (e.g. pre-stress, peak-stress) and the between factor group (losartan, placebo).

To investigate the effects of losartan on the cortisol response, we used linear regression models on the AUCg and AUCi, respectively. To control for potential drug effects on pre-stress cortisol levels, we included the baseline cortisol measurement (prior to drug manipulation) as a predictor. Further, to control for confounding factors, we included hormonal contraception to the model since it has been shown to influence cortisol secretion (Jentsch et al., 2022). Previous research has shown that age and BMI may also modulate cortisol secretion (Stalder et al., 2017). Thus, Pearson correlations were performed to first establish whether there was a correlation between BMI or age with baseline cortisol levels (prior to drug manipulation). In case there was a statistically significant association, they were included as a predictor into the linear regression model. This approach ensures that the model does not have too many predictors due to the limited sample size. In an exploratory analysis, a group x hormonal contraception interaction effect was further included into the model to investigate whether losartan intake and hormonal contraception modulate each other's potential effect on cortisol secretion.

In case the sphericity assumption was violated in any ANOVAS, a Greenhouse-Geissner Correction was applied. Similarly, if the normality assumption was violated in the independent-samples t-test, the non-parametric Welch's independent samples t-test was conducted.

5.2.6. Participant Exclusion

For three participants, technical failures during OCST presentation meant incomplete data collection. Furthermore, procedural errors were encountered with another participant, involving incorrect timing in the administration of saliva samples and questionnaires, alongside excessively noisy heart rate data. Thus, these four participants were excluded from all analyses leading to the final sample size of N = 56.

For HR and HRV analyses, three participants had missing data due to technical failures with the HR monitor. Two additional participants had to be excluded due to the presence of excessive noise in their data as highlighted by the Kubios Software Algorithm, which adjusted the sample size for the HR/HRV analyses to n = 51.

Likewise, for cortisol analyses, two participants had to be excluded: one due to intake of steroid medication and the other for having consumed food immediately before providing the pre-stress saliva sample. Consequently, the sample size for the cortisol analyses was revised to n = 54.

5.3. Results

5.3.1. Participant Characteristics

The groups were comparable across all sociodemographic, clinical, attentional, and personality trait questionnaire measures (Table 5.1.). Further, there were no acute drug effects on heart rate and systolic blood pressure (all p's > .08; Table 2). However, there was a significant group x time interaction effect on diastolic blood pressure (F (1,54) = 6.12, p = .017), which suggested that the decrease in diastolic blood pressure from baseline to peak level was more pronounced in the losartan group compared to the decrease in the placebo group (pre-peak difference placebo: M = 3.17, SD = 6.44; losartan: M = 7.37, SD = 6.25; t(53.90) = -2.48, p =.02). Nevertheless, when directly

comparing diastolic blood pressure at baseline and at drug peak level, there were no differences between the losartan and placebo group (baseline: $t(53.15) = -.04$, $p = .69$; drug peak: $t(53.02) = 1.42$, $p = .16$). In addition, there was no drug effect in cortisol levels from baseline (i.e. pre-drug administration) to pre-stress assessment (i.e. when drug peak levels were reached) ($F(1,52) = .57$, $p = .45$).

There were no acute drug effects in mood and physiological VAS ratings from baseline to drug peak level, except for the VAS item 'alert' ($F(1,54) = 6.83$, $p = .012$). Post-hoc analyses suggested that alertness decreased in the placebo group from baseline to drug peak level ($t(28) = 4.23$, $p < .001$), while it remained unchanged in the losartan group ($t(26) = 1.25$, $p = .22$). Nevertheless, a direct group comparison on the alertness at drug peak level, showed no difference between the losartan and placebo group ($t(48.88) = 0.17$, $p = .88$). For an overview, see table 2.

Neither experimenter nor participants guessed drug administration above chance level (correct experimenter = 56.7%; $p = .306$; correct experimenter = 53.3%, $p = .61$), indicating that double-blindness was preserved.

Table 5.1. Participant Characteristics. Overview of sociodemographic measures as well as attentional, clinical and personality participant characteristics in the placebo and losartan group

	Placebo (N=29; 16 female)	Losartan (N=27; 19 female)
	M (SD)	M (SD)
Sociodemographic Measures		
Age	25.48 (4.56)	23.70 (4.44)
Verbal IQ Estimate	29.22 (12.43)	34.85 (12.11)
Years of Education	17.57 (2.90)	17.19 (3.19)
Attentional, Clinical and Personality Measures		
ACS	51.76 (8.85)	54.76 (8.37)
BDI	5.62 (6.03)	7.48 (7.50)
BIS	20.66 (3.18)	20.37 (4.50)
BAS	39.48 (6.14)	41.00 (5.71)
ASI	24.45 (16.27)	25.07 (17.64)
STAI-T	39.21 (8.21)	39.96 (10.09)
EPQ – Psychosis	3.21 (2.50)	3.56 (2.34)
EPQ – Neuroticism	8.46 (3.40)	8.34 (5.27)
EPQ – Extraversion	12.00 (5.34)	12.59 (5.81)
EPQ – Lie	7.96 (4.17)	9.51 (3.01)

Note: ACS: Attentional Control Scale, BDI: Beck Depression Inventory, BIS: Behavioural Inhibition Scale, BAS: Behavioural Activation Scale, ASI: Anxiety Sensitivity Index, STAI-T: Spielberger's Trait Anxiety Inventory, EPQ = Eysenck Personality Inventory

Table 5.2. Group comparisons in physiological parameters and visual analogue scale (VAS) ratings taken before drug intake and at drug peak-level.

	Baseline		*Drug Peak Level*		
	Placebo	Losartan	Placebo	Losartan	
	M (SD)	M (SD)	M (SD)	M (SD)	p
Physiological Measures					
Heart Rate	79 (15)	77 (14)	66 (10)	65 (11)	.46
Systolic BP	119 (10)	118 (13)	113 (9)	109 (10)	.20
Diastolic BP	72 (8)	73 (8)	69 (9)	66 (9)	.02
VAS Rating					
Anxious	17.24 (18.36)	12.05 (16.06)	8.25 (9.57)	8.53 (12.31)	.13
Sleepy	24.43 (24.88)	19.33 (22.68)	26.83 (27.23)	25.22 (24.78)	.48
Flushed	11.61 (16.60)	7.99 (11.65)	3.30 (6.41)	5.15 (10.90)	.06
Tearful	3.97 (7.14)	4.19 (6.99)	1.58 (3.38)	2.75 (6.13)	.55
Nauseous	1.85 (3.99)	3.76 (8.55)	1.11 (2.83)	2.99 (5.80)	.99
Hopeless	6.10 (11.89)	4.17 (7.72)	4.33 (13.35)	2.37 (4.35)	.99
Tremor	1.89 (2.94)	2.76 (6.73)	1.23 (2.66)	1.63 (3.40)	.76
Sad	7.00 (9.73)	7.37 (11.60)	4.71 (9.20)	3.05 (5.47)	.25
Dizzy	1.96 (4.31)	2.74 (7.19)	1.92 (3.39)	6.02 (13.06)	.08
Depressed	4.42 (10.18)	3.23 (5.79)	2.67 (5.00)	2.51 (5.56)	.56
Heart Racing	7.59 (13.57)	5.64 (12.74)	1.88 (3.15)	4.28 (9.86)	.08
Alert	40.75 (24.10)	28.70 (26.88)	26.69 (22.00)	25.61 (28.50)	.01

Note: Heart rate is presented in bpm. Systolic and diastolic blood pressure are presented in in mmHg. p-values refer to the statistical level of significance of group x time interaction effect.

5.3.2. Manipulation Check

Behavioural Task analysis. Behavioural results suggest that both groups expectedly showed low task performance across the three domains with accuracy scores below 50%, as presented in detail below.

Mental Arithmetic Task. Mental arithmetic equations were presented across three blocks during the OCST. Mixed models ANOVAs with the between factor group (losartan, placebo) a within-factor block (block 1, block 2, block 3) showed that the difficulty level of the equations increased over

blocks (main effect block $F(1.66, 89.40) = 196.40$, $p < .001$), while participants' accuracy decreased over blocks (main effect block $F(1.86, 100.29) = 181.26$, $p < .001$). This was expected, as the difficulty level from the previous block was maintained at the start of the subsequent block. Similarly, reaction times for correct responses in both groups increased over blocks (main effect block $F(1.48, 80) = 40.30$, $p < .001$), which aligns with the mental arithmetic equations becoming more challenging due to the increasing difficulty level.

There were no differences in behavioural task performance between the losartan and placebo group, as measured in difficulty level, accuracy and reaction times (main effect group, all F's < 1.86, all p's> .178; group x block interaction all F's < .11, all p's > .31). That is, both groups reached similar mean difficulty levels throughout the task (placebo: $M = 2.80$ $SD = 0.44$; losartan: $M = 2.88$; $SD = 0.46$) and achieved similar accuracy scores below 50 % (placebo: $M = 47.74\%$ correct, $SD = 6.11$; losartan $M = 47.05\%$ correct, $SD = 4.47$). In addition, both groups had similar reaction times for correct responses across the task (placebo: $M = 3.06$ seconds, $SD = 0.72$; losartan: $M = 2.83$ seconds, $SD = 0.54$).

Anagram Task. Anagrams were presented in one block during the OCST, and task performance was investigated. There were no group differences in either accuracy (placebo: $M = 18.41$ % correct, $SD = 10.15$; losartan: $M = 21.00$ % correct, $SD = 18.53$; $t(39.67) = -.64$, $p = .53$), nor in their reaction times for correct responses across groups (placebo $M = 18.27$ seconds, $SD = 39.93$; losartan $M = 17.05$ seconds, $SD = 43.11$, $t(46.36) = 1.02$, $p = .31$). As all participants were presented the same anagrams, there was no measure of difficulty level.

Visual Search Task. The Visual Search Task was presented in one block. Both groups achieved a similar mean level of difficulty (placebo: $M = 1.52$, $SD = 0.51$; losartan: $M = 1.74$, $SD = 0.59$; $t(51.74) = -1.45$, $p = .15$) and both

groups achieved a similar accuracy score (placebo: *M* = 40.63 % correct, *SD* = 7.87, losartan: 43.93 % correct, *SD* = 8.46; *t*(52.90) = -1.51, *p* = .14).

Stress Deception. Out of 56 participants included in data analysis, 38 (67.86%) correctly guessed the nature of the stress deception, potentially confounding the results on the stress response in general. Importantly, there were no group differences in correctly guessing the stress deception (placebo 20 correct (68.97%); losartan 18 correct (66.67 %); *t*(52.36) = -0.02, *p* = .98).

5.3.3. The Effect of ARBs on the Stress Response

Subjective Stress Response. Subjective stress was reflected using the VAS item 'stressed' and STAI-S score, pre- and post-stress induction. A mixed model ANOVA with the within factor time (pre-stress, peak-stress) and the between factor group (losartan, placebo) showed that subjective VAS rating increased from pre-stress to post-stress across both groups (placebo: pre-stress *M*= 13.99; *SD* = 21.29, post-stress *M* = 41.41, *SD* = 35.36; losartan: pre-stress M = 13.85, *SD* = 20.39, post-stress *M* = 39.24, *SD* = 32.34; *F* (1,54) = 45.15, *p* < .001). Similarly, STAI-S increased from pre-stress test to post-stress in both groups (Placebo: pre-stress *M* = 32.49, *SD* = 8.52; post-stress *M* = 43.41, *SD* = 12.31; Losartan pre-stress *M*=32.22, *SD* = 9.29; post-stress *M* = 45.33, SD = 11.76; *F* (1, 52.06) = 77.58, *p* < .001). This indicates that both groups subjectively felt more stressed and anxious after the OCST.

However, there was no main effect of group, nor group x time interaction effect on the VAS item 'stressed' (both *F*'s (1,54) < .07; both *p*'s > .798, figure 5.4.-A). Similarly, there was no group effect, or group x time interaction effect on the STAI-S, both *F*'s (1, 52.06) < .64; both p's > .43, figure 5.4.-B). Together, these results indicate that losartan had no effect on the subjective stress response.

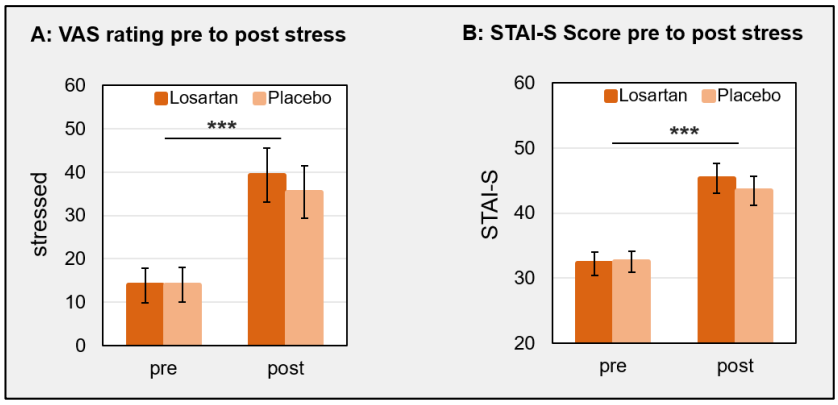


Figure 5.4. Subjective Stress Response. When comparing subjective ratings pre and post stress, participants across both groups reported to be more stressed after the stress task. There were no group differences. *** p<.001

Heart Rate (HR) and Heart Rate Variability (HRV). The time (pre-stress, during stress) x group (losartan, placebo) mixed model ANOVA showed that HR increased during the task in both groups (pre stress: placebo *M* = 65.53, *SD* = 9.10, losartan *M* = 64.97, *SD* = 9.43; during stress: placebo *M* = 69.38, *SD* = 10.29, losartan *M* = 73.90, *SD* = 13.56; main effect time: *F*(1,49) = 34.38, *p*<.001). However, the corresponding mixed-model ANOVA on the HRV, showed that LF/HF did not differ between pre-stress and during stress task (pre stress: placebo *M* = 1.29, *SD* = 1.15, losartan *M* = 1.49, *SD* = 1.34; during stress: placebo *M* = 1.55, *SD* = 0.88, losartan *M* = 1.96, *SD* = 1.57; main effect time: *F* (1,49) = 2.26, *p* =.14), suggesting that the OCST did not modulate HRV which is a marker of SNS activity.

In addition, there was no significant main effect of group (*F* (1,49) = .23, *p* = .63), nor group x time interaction effect (*F* (1,49) = 3.65, *p* = .06), indicating that losartan did not affect HR response. Notably, the group x time interaction effect emerged as a non-significant trend indicating a greater increase in HR in the losartan group compared to placebo during the stress task. However, the HR increase in both groups remains small and comparable (see figure 5.5. for visualisation of M/SD and for a minute-by-minute overview of HR).

In addition, there was no main effect of group ($F(1, 49) = 1.03$, $p = .31$), nor group x time interaction effect ($F(1, 49) = .12$, $p = .73$) on the LF/HF ratio. This indicates that ARB administration did not modulate SNS activity reflected by HRV response.

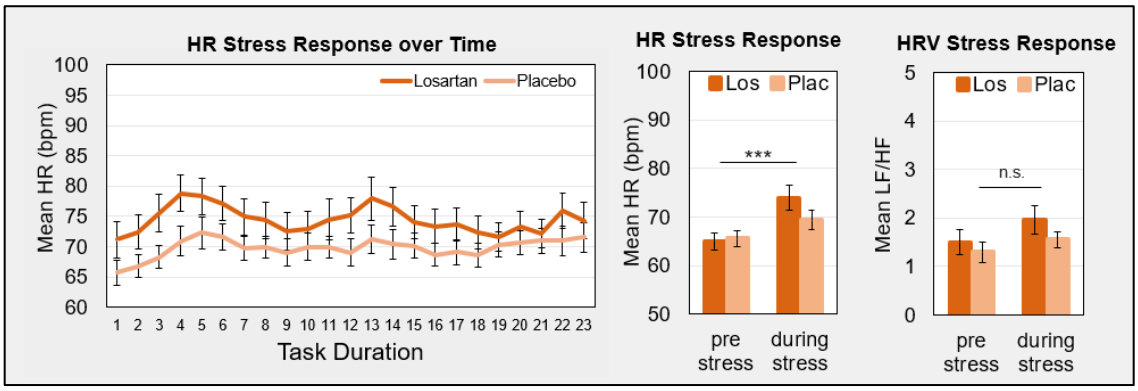


Figure 5.5.: Physiological Stress measures reflected by Heart Rate (HR) and Heart Rate Variability (HRV). **Left:** Minute to Minute overview of HR over the course of the stress task. **Right:** Mean HR and HRV response. HRV was reflected by the 'low frequency/high frequency (LF/HF)' ratio. While HR increased during the task across groups, HRV remained unchanged. There were no effects of losartan. Los = losartan, Plac = placebo; *** p < .001

5.3.4. Salivary Cortisol Response. To describe the course of cortisol secretion, a repeated measures ANOVA across both groups was used, with the within factor time (pre-stress, peak-stress, 20min post stress, 40 min post stress) showing that cortisol secretion changes over the course of the assessment points ($F(1.77, 90.40) = 16.82$, $p < .001$). Paired samples t-tests across both groups showed that cortisol levels increased from the pre-stress to peak-stress assessment ($t(53) = -4.928$, $p < .001$), and then remained stable from peak-stress to 20min post-stress ($t(53) = -1.227$, $p = .23$), and from 20min post-stress to 40min post-stress ($t(52) = -1.51$, $p = .14$; see figure 5.6. for overview). This suggests that the OCST elicited an HPA-axis response.

To assess drug induced group differences, linear models on AUCg and AUCi were fitted. Prior correlational analyses on potential confounding factors showed that baseline cortisol levels were significantly associated with age (r =-.35, p = .01) and BMI (r = -.33, p =.02). Thus, these two factors were included in the linear regression model to control for potential influences (figure 5.7). This results in the final model AUC = cortisol pre drug manipulation + BMI + Age + hormonal contraception + group. The linear regression model showed that losartan administration had no effect on measures of cortisol response (AUCg: *beta* = -0.04, *CI* = [-0.16, 0.09], p = .53; AUCi: *beta* = 0.04, *CI* = [-0.23, 0.31], p =.76; figure 5.5.; for an overview of all predictor values, see table 5.3.).

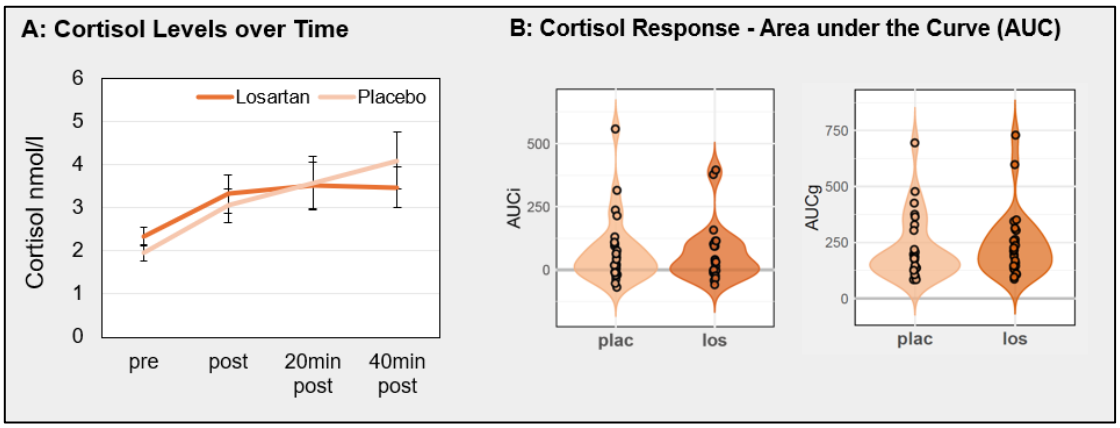


Figure 5.6. Endocrine stress response reflected by salivary cortisol levels. Cortisol levels and AUC measures are presented in their original unit for visualisation purposes. **A:** Cortisol levels over the course of assessment points. Across both groups, cortisol levels significantly increased from the pre-stress to the post-stress assessment, and then remained stable. **B:** There were no group differences in either AUCi or AUCg measures. Los: Losartan, Plac: Placebo.

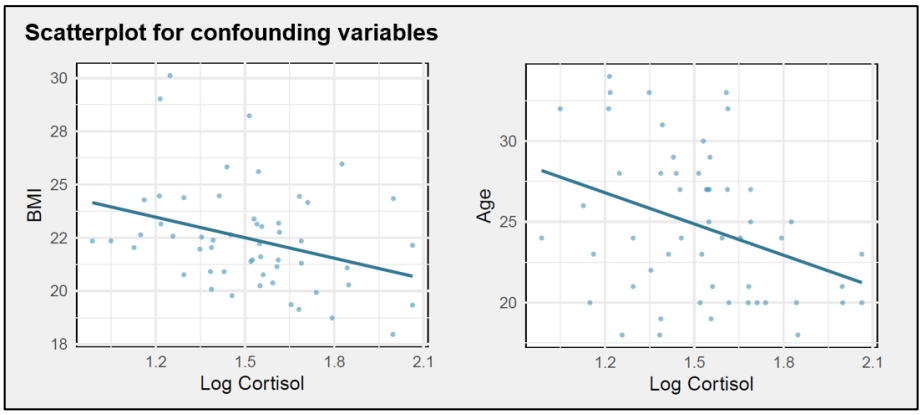


Figure 5.7. Scatterplots underlying significant correlations between baseline cortisol (pre drug administration) and BMI (r = -.33) and age (r =-.35), respectively.

Table 5.3. Overview Model Parameters for Main Cortisol Analysis

Predictors	AUCg				AUCi			
	β	95 % CI	p		β	95 % CI	p	
Baseline Cortisol	.39	[.14, 4.11]	.003	**	-.07	[-.61, .47]	.79	
BMI	-.01	[-.04, .02]	.42		-.007	[-.07, .05]	.80	
Age	-.01	[-.02, .004]	.15		-.01	[-.04, .02]	.43	
Hormonal CC	-.11	[-.25, .02]	.10		-.39	[-.68, -.09]	.01	**
Group	-.04	[-.16, .09]	.53		.04	[-.23, .31]	.76	

Note. hormonal CC: hormonal contraceptives. AUCg: area under the curve with respect to ground. AUCi: area under the curve with respect to increase.

5.3.5. Exploratory Analyses

To explore potential interactions between losartan administration and hormonal contraception intake, an exploratory analysis was conducted by adding the 'group x hormonal contraception' interaction effect into the linear models above (full model: AUC = cortisol pre drug manipulation + BMI + Age + hormonal contraception + group + group x hormonal contraception).

While hormonal contraception was significantly associated with AUCi (beta =

-0.86, CI [-1.27, -0.46], p < .001) and there was a trend-level association with AUCg (*beta* = -.20, CI [-0.41, 0.01], *p* = .06), there was further a significant interaction effect between drug group and hormonal contraception intake on AUCi (*beta* = 0.84, CI [0.30, 1.38], *p* = .003; for details on all predictor values see table 5.4.). That is, women on hormonal contraceptives showed a blunted cortisol response reflected by AUCi, which seemed to be counteracted by losartan intake (see, figure 5.8.).

Acknowledging that only women can take hormonal contraceptives, analyses were repeated on female participants only (n = 33; placebo total n = 15, hormonal contraception n = 5; losartan total n = 18, hormonal contraception n = 7). The results remained unchanged (see table 5.4. for all predictor values).



Figure 5.8. Exploratory Analysis – Interaction between ARBs and Hormonal Contraception Intake in Women. For visualisation and to retain interpretability, AUCi (area under the curve with respect to increase) is presented prior to being log-transformed here. An AUCi of 0 indicates that cortisol levels did not increase in response to stress. While women on hormonal contraception show a blunted cortisol response, it seemed to be partially restored by losartan intake.

Table 5.4. Overview of Regression Model Parameters of the Explanatory Analysis

Predictors	AUCg				AUCi			
	β	95 % CI	p		β	95 % CI	p	
All participants								
Baseline Cortisol	.39	[.14, .64]	.003	**	-.04	[-.53, .45]	.88	
BMI	-.01	[-.04, .01]	.36		-.02	[-.07, 04]	.56	
Age	-.01	[-.02, .004]	.15		-.01	[-.03, .02]	.41	
Hormonal CC	-.20	[-.41, .005]	.06		-.86	[-1.26, -.46]	<.001	***
Group	-.08	[-.22, .06]	.28		-.17	[-.45, .11]	.23	
Group x Hormonal CC	.15	[-.12. -.43]	.26		.84	[.30, 1.38]	.003	**
Women only								
Baseline Cortisol	.49	[-.14, .83]	.007	**	.11	[-.70, .92]	.79	
BMI	-.01	[-.05, .02]	.46		-.02	[-.11, .06]	.57	
Age	-.01	[-.03, .02]	.52		-.001	[-.05, .05]	.98	
Hormonal CC	-.13	[-.50, .04]	.09		-.98	[-1.61, -.34]	.004	**
Group	-.23	[-.38. .12]	.28		-.38	[-.96, .20]	.19	
Group x Hormonal CC	.20	[-.15, .55]	.24		1.05	[.23, 1.87]	.01	**

Note. hormonal CC: hormonal contraceptives. AUCg: area under the curve with respect to ground. AUCi: area under the curve with respect to increase.

5.4. Discussion

This study investigated the effects of ARBs on the human stress response using subjective and biological stress markers. Stress was induced using a performance stress paradigm, which consisted of mental arithmetic tasks, an anagram task and a visual search task. In response to the stress paradigm, there was an increase in subjective stress ratings, HR and cortisol response, while the HRV remained unaffected. This suggests that performance-related stress modulated subjective, physiological and HPA-axis stress response, while not affecting the SNS stress response. In addition, there was no effect of ARB intake in any of the subjective, HR, HRV nor cortisol measures. Nevertheless, the exploratory analyses showed that ARB administration

elicited a cortisol response in hormonal contraceptive users, which was blunted otherwise.

While previous research has shown that ARBs modulate the stress response in rodents, this study took a first step to translating such findings into a human population. This is particularly important since stress is suggested to be a key modulator for PTSD psychopathology – for instance through its modulatory role on episodic memory formation (de Quervain et al., 2017; Pitman et al., 2012).

In this study, the OCST was used as a stress manipulation. While not a direct analogue to traumatic stress, the OCST was designed to align with the most prominent stress paradigm aimed to provoke HPA-axis activity - the Trier Social Stress Test (TSST Kirschbaum et al., 1993). Its distinctive feature is the computerised format, which bypasses the need of human actors for its administration.

5.4.1. A lack of Direct ARB Modulation on the Cortisol Response

While the OCST provoked cortisol responses and participants reported an increase in their subjective stress ratings, there was no group difference between the losartan and placebo group. These results contrast previous findings in animal research which have shown that ARBs decreased corticosteroid secretion (Wincewicz et al., 2016) – the rodent equivalent to human cortisol – alongside reducing HPA-axis activity more generally (Armando et al., 2007; Pavel et al., 2008). However, such animal studies have used chronic ARB administration and prolonged stress exposure. For instance, in one study, rodents were exposed to 21 days of restrained stress, while simultaneously being treated with ARBs (Wincewicz et al., 2016). Similarly, rodents were given ARBs for two weeks, prior to being exposed to 24 hrs of isolation stress (Armando et al., 2007). Thus, it is possible that prolonged ARB administration is required to modulate cortisol responses to

acute stress, and/or that ARBs modulate basal cortisol levels during prolonged stress exposure only. Particularly, the latter would require the assessment of different cortisol markers, such as the cortisol awakening response as a marker of short-term basal cortisol secretion (Fries et al., 2009), or hair cortisol concentrations as a marker of long-term cortisol secretion (Stalder & Kirschbaum, 2012).

5.4.2. Interactions between ARBs and Hormonal Contraceptives

In addition, this chapter included an exploratory analysis to examine potential interaction effects between ARBs and hormonal contraception on the cortisol stress response. This was informed by the established direct effect of hormonal contraception on cortisol response (Jentsch et al., 2022), and the RAS being modulated by oestrogen activity (Hilliard et al., 2013; Komukai et al., 2010). Consistent with previous research, our results show that the cortisol stress response is blunted in hormonal contraception users (for meta-analysis, see Gervasio et al., 2022). In addition, there was an interaction effect between ARB intake and hormonal contraception intake on the cortisol response. That is, losartan seemed to specifically increase the cortisol response of hormonal contraception users with no effect among non-users. Thus, our results may indicate that ARBs specifically restore the blunted cortisol response induced by hormonal contraception intake.

Overall, the relationship between hormonal contraception and HPA-axis functioning is multifaceted. For instance, it has been consistently shown that total cortisol levels are elevated in hormonal contraceptive users (Ågren et al., 2011; Hertel et al., 2017; Kangasniemi et al., 2022; Klipping et al., 2021), which suggests a condition similar to prolonged stress exposure (Hertel et al., 2017). Conversely, the cortisol response to acute stress is blunted (for meta-analysis, see Gervasio et al., 2022). These effects are attributed to the role of oestrogen in hormonal contraceptives stimulating corticosteroid-binding-globulin (CBG) synthesis (Wiegratz et al., 2003). Since CBG binds cortisol, it

has been suggested that a compensatory increase in cortisol secretion is required to maintain sufficient levels of free, biologically active cortisol (Kumsta et al., 2007). However, this leads to a shift in the ratio of free to bound cortisol, and an increase in total cortisol levels (Hellhammer et al., 2009). As a result, the increased cortisol levels inhibit CRH release, which would normally initiate the HPA-axis cascade in response to acute stress (Hellhammer et al., 2009).

Due to the interaction between hormonal contraception and ARB administration in this study, our results suggest that the RAS may modulate oestrogen regulation of the cortisol response. Alternatively, the potential effect of ARBs to restore a blunted stress response may extend beyond the context of hormonal contraception – addressing individuals at risk for stress-related disorders and PTSD more generally. For instance, a blunted cortisol stress response has been associated with higher trait anxiety (Jezova et al., 2004), cumulative lifetime stress (Lam et al., 2019) and PTSD diagnosis (Metz et al., 2020). Either way, these findings highlight the need for further investigation into the mechanistic pathways involved.

A significant caveat of our study design is that only a small number of participants were taking hormonal contraception (12 out of 35 women). Thus, our results need to be considered very preliminary, and they require replication in a larger cohort in hypothesis-driven research. Further, it needs to be investigated whether there is a general interaction between hormonal contraception and ARB intake on other PTSD-related biological and neurocognitive markers, or whether this interaction involves the cortisol response exclusively. Notably, initial evidence suggests an association between hormonal contraception intake and more intrusive memories in PTSD patients (Maslahati et al., 2023).

5.4.3. Understanding the lack of ARB Effects on Heart Rate Measures

With regards to the HR and HRV responses, there was no effect of ARB administration. This contrasts previous research on the trauma film paradigm, which has shown that a single dose of losartan prevented an increase of HR and the LF/HF ratio of HRV while watching distressing film clips of traumatic events (Shkreli et al., 2020). However, the OCST used in this study did not modulate HRV response reflected by the LF/HF ratio (Rajendra Acharya et al., 2006), a marker of the ratio between SNS activity (via low frequencies) and PNS activity (via high frequencies). Thus, SNS activity which is important for fear memory and the fight and flight reaction (Azevedo et al., 2024; Schwabe et al., 2022), seems unaffected in the current study.

Furthermore, the nature of stress induced by the OCST differs from that of film exposure to traumatic events, typically used to simulate a PTSD-related stressor. In contrast, the OCST was designed to induce performance stress and consists of cognitive demanding tasks, which may be more relatable to daily stressors rather than traumatic stress. In particular, the OCST not only lacks the element of fear but also unpredictability and uncontrollability compared to the trauma film paradigm, which may evoke lower stress responses. This is not only reflected by the lack of LF/HF ratio increase in response to the OCST, but also the HR response was lower compared to our previous trauma-film study. To illustrate, the HR in the placebo group rose from approximately 70 bpm during baseline, to 90 bpm during trauma film exposure (Shkreli et al., 2020). In contrast, in response to the OCST, HR increased from 66 bpm during baseline to 69 bpm. Taken together, this highlights that performance stress, as induced by the OCST, may not evoke stress responses as intense as those associated with trauma film exposure, which may have limited the potential of ARB action.

Similarly, previous studies in rodents have shown that ARBs reduce anxiety-like behaviour (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012), while our work has shown that losartan prevented an increase of HR and LF/HF ratio during exposure to distressing film material (Shkreli et al., 2020). In contrast, this present study demonstrates that ARBs do not modulate HR and LF/HF ratio in response to performance stress. This divergence suggests that the effects of ARBs on the stress response may be limited to stressors directly associated with fundamental instincts such as anxiety and fear and may not translate to general stressors.

5.4.4. Limitations and Future Directions

This study has some limitations. First, the stress induction in this study is not directly relatable to trauma exposure and may therefore only offer limited insights into mechanism involved in PTSD development. Instead, the OCST is primarily related to cognitive and performance stress, which rather resembles an every-day stressor than a traumatic experience. Second, single-dose administration of 50mg losartan reduced diastolic blood pressure. Although such effect was not observed in any of the previous studies in our group (e.g. Pulcu et al., 2019; Reinecke et al., 2018; Shkreli et al., 2020; Zika et al., 2024) we cannot completely rule out that this physiological effect could have confounded our results. Finally, a considerate number of participants correctly anticipated the deceptive nature of the task (n = 38, 67.86 %). Particularly, they noticed that their suggested low performance in comparison to the 'general population' seemed implausible, and that the negative feedback seemed too harsh to be genuine. Anticipating the deception may have not only biased their stress responses but also their commitment to performing the task. That is, although their cortisol response and subjective stress ratings increased, it remains uncertain whether unawareness of the deception would have led to more pronounced effects. In addition, this study was not preregistered.

In conclusion, previous research has shown that ARBs reduced HPA-axis activity in rodent models (Armando et al., 2001; Armando et al., 2007; Pavel et al., 2008), and that they reduced HR and the LF/HF ratio of HRV in humans while watching distressing film clips (Shkreli et al., 2020). However, this study did not observe comparable effects in the context of performance-related stress. Thus, our study indicates that potential ARB effects on the stress response, may not extend universally across all stress types, but rather involve stressors associated with fear and anxiety. We further highlight a potential role of ARBs to restore a blunted cortisol stress response, which needs targeted investigation and replication in a larger cohort.

6

Chapter 6
General Discussion

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Key abbreviations

CBG: Corticosteroid-Binding-Globulin

CRF/CRH: Corticotrophin Releasing Factor/Hormone

IFG: Inferior Frontal Gyrus

PHC: Parahippocampal Gyrus

SNS: Sympathetic Nervous System

General Discussion

6.1. Overview

This DPhil thesis aimed to investigate key mechanisms of neurocognitive ARB action which may be relevant for PTSD psychopathology. Using a series of double-blind placebo-controlled experiments with a single dose of losartan, this thesis particularly focuses on memory formation, hippocampal functioning, resting state functional connectivity and markers of the human stress response.

This research builds up on previous work aimed to translate key findings of central ARB action from animal models to human research. It extends this work by investigating neurocognitive processing beyond fear learning and reward processing – which has been the focus of most human studies to date.

Chapter 2 and 3 investigated ARB effects on memory formation. While chapter 2 shows that a single dose of losartan increased PHC activity during an episodic memory task with images of animals and landscapes, chapter 3 highlights that a single dose of losartan also leads to more stable activity patterns in the PHC during the task. Together these results indicate that ARBs may increase higher-order visual processing during memory formation, as the PHC is a key input area to the hippocampus at the end of the ventral visual stream.

Chapter 4 focused on resting state functional connectivity analyses, using predefined seeds within the memory system (hippocampus, PHC) and within the fear system (amygdala, anterior insula), alongside data-driven ICA. Results showed that losartan decreased functional connectivity between the hippocampus and the IFG, which is part of the salience network. This may reflect a decreased influence of emotional valence on memory encoding mechanisms. Similarly, results showed a decreased functional connectivity

between the PHC and DLPFC, potentially reflecting a disengagement of cognitive control during higher-order visual processing. There were no effects of ARB administration on rsFC using ICA.

In addition, Chapter *5* examined the role of ARBs on biological and subjective markers of the stress response. This chapter showed that a single dose of losartan did not influence the response to performance stress, but that it may restore the blunted cortisol response seen in hormonal contraceptive users. This highlights the interaction of the RAS and oestrogen, which warrants targeted investigation.

Taken together this DPhil research supports the role of ARBs as promising modulators of brain function, with potentially important implications on PTSD psychopathology, which will be discussed in detail here.

This general discussion chapter begins with a brief revision on the key neurocognitive processes implicated in PTSD psychopathology, including core ARB effects. Subsequently, the current neuroimaging results and the results of the stress chapter will be discussed more in-depth – concluding with an integration into the broader neurocognitive ARB literature and potential mechanistic insights relevant to PTSD.

Moving forward, challenges and directions for establishing mechanistic pathways of central ARB action will be discussed, followed by practical considerations for future ARB research.

6.2. Revisiting Neurocognitive Processes in PTSD and Core ARB Effects

In general, PTSD development is characterised by neurocognitive changes due to extreme stress levels at trauma exposure. While perceptual processing of low-level visual cues is exaggerated during trauma exposure, processing of contextual information is impaired, so that the traumatic experience is

dysfunctionally integrated into the episodic memory system (Brewin, 2014; Brewin et al., 2010). As a result, perceptually similar cues can trigger re-experiencing symptoms such as memory intrusions, leaving patients with a pervasive sense of threat (Ehlers & Clark, 2000).

Consequently, after disorder onset, patients with PTSD are characterised by aberrations in core neurocognitive mechanisms. For instance, patients with PTSD show alterations in visual processing which manifest as enhanced priming response to trauma-relevant cues (Ehring et al., 2011; Kleim et al., 2012). In addition, patients with PTSD exhibit elevated psychophysiological responses to threat as well as deficits in fear extinction and threat/safety differentiation, alongside hyperactivation of limbic system like the amygdala (Fitzgerald et al., 2018; Jovanovic et al., 2012; Van Elzakker et al., 2014). Further, patients with PTSD are characterized by deficits in inhibitory control, primarily mediated via vmPFC processing (Polak et al., 2012). Ultimately, aberrations in episodic memory are present in patients with PTSD (Petzold & Bunzeck, 2022), as well as structural and functional changes in hippocampal functioning (Joshi et al., 2020; Logue et al., 2018; O'Doherty et al., 2015) (for detailed overview see chapter 1 – General Introduction).

Previous work in animals and humans has shown that ARBs can modulate some of these neurocognitive processes including their associated brain structures. However, such research has primarily centred around domains which are relevant to both PTSD and anxiety development, potentially given that population-based studies have shown protective effects of ARB intake on PTSD symptom development (Khoury et al., 2012; Seligowski et al., 2021), while animal models have shown direct anxiolytic effects after ARB administration (de los Angeles Marinzalda et al., 2014; Genaro et al., 2017; Llano López et al., 2012). For instance, it was shown that ARBs reduce aversive learning (Pulcu et al., 2019; Xu et al., 2022; Zhou et al., 2023; Zika et al., 2024), enhance extinction learning (Marvar et al., 2014; Zhou et al., 2019)

and facilitate amygdala processing during safety/threat discrimination of facial expressions (Reinecke et al., 2018).

However, in contrast to anxiety disorders, core PTSD symptoms include memory aberrations such as involuntary memories of the traumatic event (American Psychiatric Association, 2013). In addition, decreased memory performance for neutral and emotional material has been primarily reported in PTSD (Brewin et al., 2007; Carrión et al., 2010; Hayes et al., 2011; Noriega et al., 2021; Samuelson, 2011), while PTSD is characterized by functional and structural hippocampal changes – most prominently reduced hippocampal volumes (Joshi et al., 2020; Logue et al., 2018; O'Doherty et al., 2015). Similarly, changes in the SNS stress response and HPA-axis actively are primarily associated with PTSD (e.g. Ehlers et al., 2010; Pole et al., 2009; Steudte-Schmiedgen et al., 2016; Suendermann et al., 2010).

Thus, this DPhil research extended previous human work by examining neurocognitive processes that are directly relevant to PTSD and more distinct from general anxiety processes, such as memory formation and the stress response.

6.3. Implications of the Neuroimaging Results

In this DPhil thesis, two chapters focused on memory formation. Previous work in animal models has shown that ARBs modulate hippocampal functioning (Bild et al., 2013; Coatl-Cuaya et al., 2022; Hosseini et al., 2021), while regular ARB intake was associated with memory enhancement in elderly humans (Fogari et al., 2003; Fogari et al., 2006). Thus, a behavioural effect of improved memory performance, alongside a facilitation of hippocampal functioning was expected in chapter 2 and 3. However, in contrast to hippocampal functioning, our results highlight that PHC functioning may be particularly modulated by ARB action, since PHC mean activity was greater (chapter 2) and PHC activity patterns were more stable

(chapter 3) after losartan administration during memory encoding of novel images and visual processing of familiar images.

This sub-chapter starts with an outline of the role of the PHC in PTSD and a discussion on whether ARBs act directly or indirectly on the PHC based on AT1 receptor localisation. Subsequently, reasons for the lack of ARB effects on the hippocampus and behavioural memory performance are evaluated. This is followed by a discussion on the role of the hippocampus beyond memory formation and what this may imply for appropriate task selection in future ARB research. This sub-chapter concludes with insights from resting state studies overcoming limitations on task selection.

6.3.1. The Parahippocampal Gyrus in PTSD

The PHC is part of the ventral visual stream and deeply involved in higher-order visual processing (Dwivedi et al., 2021; Eichenbaum & Lipton, 2008; Epstein et al., 2003; Mohsenzadeh et al., 2020). For instance, within the PHC, there is the parahippocampal place area which is specifically involved in processing complex visual scenes by integrating information about the spatial layout, objects, and context within a scene (such as naturalistic pictures of animals and landscapes) (Dwivedi et al., 2021; Epstein, 2005; Epstein et al., 2003). The PHC is closely connected to the hippocampus and the interaction of these two brain areas is crucial for memory formation within the medial temporal lobe, i.e. visual scenes and spatial information (from the PHC) are integrated into episodic memories (in the hippocampus) (Eichenbaum et al., 1996; Moscovitch et al., 2016). Accordingly, a broad body of research has shown that PHC and hippocampus mean activity and activity pattern similarity were associated with successful memory formation (Chen et al., 2017; Oedekoven et al., 2017; Ritchey et al., 2013; Staresina et al., 2011; Staresina et al., 2012; Xue et al., 2010).

While basic neurocognitive research on memory formation widely acknowledged the joint role of HC and PHC, and the more wider term 'medial temporal lobe' is often used (e.g. Eichenbaum & Lipton, 2008), clinical research in PTSD has primarily centred around the hippocampus as the core brain structure for memory formation. However, despite the hippocampus being investigated more frequently in PTSD research, there is increasing evidence on the importance of PHC functioning.

In line with structural work on the hippocampus, it has been consistently shown that PTSD patients exhibit smaller PHC volumes compared to trauma-exposed controls without PTSD diagnosis (e.g. Basavaraju et al., 2021; Nardo et al., 2010; Zhang et al., 2011), which was further confirmed by meta-analytic evidence (Del Casale et al., 2022). While greater symptom severity in PTSD patients was associated with decreased PHC volume (Aupperle et al., 2013), PHC volumes increased after PTSD treatment (Bossini et al., 2017). Together, these results indicate that the PHC may be a relevant structure for PTSD psychopathology and involved in treatment response.

Greater re-experiencing symptoms in PTSD patients correlated with decreased cortical thickness in the PHC (Crombie et al., 2021). This is particularly interesting, as attenuated activity in higher-order visual areas – like the PHC and fusiform gyrus – have been associated with increased perceptual priming response (Blondin & Lepage, 2005; Lee et al., 2020; Soldan et al., 2010), which has been implicated as a mechanism to underlie memory intrusion development (Sündermann et al., 2013). Indeed, PTSD patients exhibit elevated perceptual priming response for trauma-related cues (Ehring et al., 2011; Kleim et al., 2012). Nevertheless, functional neuroimaging studies investigating the priming response in PTSD patients are necessary to confirm the suggested role of the PHC.

In functional work, meta-analyses have consistently shown that PHC function distinguishes PTSD patients from controls (Lee et al., 2021; Patel et

al., 2012; Stark et al., 2015). However, those meta-analyses included different control groups and summarised functional brain activity of PTSD patients across a variety of cognitive tasks. Thus, the exact manifestation of PHC activity differences in PTSD patients remains inconclusive, particularly since the results of the meta-analysis are heterogeneous in terms of direction (i.e. whether patients with PTSD show elevated or attenuated activity). For instance, one meta-analysis compared PTSD patients to trauma-exposed controls and showed that PHC activity across emotional processing paradigms is decreased in PTSD patients (Patel et al., 2012). In contrast, another meta-analysis showed that alterations in PHC activity distinguish PTSD patients from trauma-exposed and healthy controls but did not confirm a direction of elevated or attenuated activity (Stark et al., 2015). The third meta-analysis showed elevated PHC activity in response to emotional paradigms in PTSD patients (Lee et al., 2021). However, they did not differentiate between trauma-exposed and healthy controls, but treated them as a single control group instead. Thus, the role of the PHC in PTSD-related emotional processing seems to depend on careful task and control group selection.

In addition to task and control group selection, an additional reason for the heterogeneity in functional PHC results may be that previous studies have not consistently corrected for grey matter volume. Such correction is particularly relevant given that grey matter volumetric differences in the PHC are present in patients with PTSD (for meta-analysis, see Del Casale et al., 2022), thus potentially confounding brain activity. On the other hand, it may be important to extend previous research with multivariate fMRI analysis, such as Pattern Similarity Analysis (PSA), to gain a more-fine graded understanding of PHC involvement in PTSD.

Taken together, the role of the PHC in PTSD seems to become increasingly evident, but targeted studies are required to understand the mechanistic underpinnings. In this DPhil research, the modulatory role of ARBs on the

PHC has been shown in all fMRI analysis chapters. Since the PHC is involved in higher-order visual processing and memory (Aminoff et al., 2013; Dwivedi et al., 2021; Epstein et al., 2003), and since ARB intake facilitated PHC processing, it can be speculated that ARBs may contribute to PTSD prevention via facilitating a functional integration of visual cues during trauma exposure into the episodic memory system. On the other hand, decreased PHC activity has been associated with a greater perceptual priming response (Blondin & Lepage, 2005; Soldan et al., 2010), and perceptual priming has been implicated to underlie memory intrusion development (Ehlers et al., 2004; Sündermann et al., 2013). Thus, the ARB-induced increase in PHC processing may speculatively contribute to PTSD prevention via attenuating perceptual priming which in turn may lead to reduced memory intrusion development.

However, given that the study underlying chapter 2 and chapter 3 was chosen to investigate memory formation and hippocampal functioning, the interpretation of the PHC results remains post-hoc and should be treated with caution. Thus, it is important in future research to design experiments which target PHC function and higher-order visual processing, specifically. For instance, such tasks may include images of faces versus houses which have been often used in basic neurocognitive research, since faces are uniquely processed in the fusiform face area, while houses are distinctively processed in the parahippocampal place area (Keizer et al., 2008; Summerfield, Egner, et al., 2006; Wang et al., 2019).

6.3.2. Can ARBs directly modulate PHC activity via AT1 Receptors?

This thesis showed that ARBs modulate PHC activity and stability, while potential underlying mechanisms relevant to PTSD have been discussed. However, to advance a mechanistic understanding it remains to be established whether ARBs can act directly or indirectly on the PHC – given

that it is currently unknown whether angiotensin-II receptors are expressed in the PHC.

ARBs can primarily bind on AT1 receptors, which are expressed throughout the brain. However, studies on the specific localisation of AT1 receptors have predominantly been carried out in rodents and were mainly conducted in the 1990s (for review, see Allen et al., 1998).

The parahippocampal region (the rodent equivalent to the human PHC) consists of the perirhinal, postrhinal and entorhinal cortex (Furtak et al., 2007). Indeed, AT1 receptors have been localised in the rodent entorhinal cortex as well as in other adjacent areas such as the piriform cortex and hippocampus (von Bohlen und Halbach & Albrecht, 1998). Notably, the entorhinal cortex also exists in the human brain (located adjacent to the hippocampus and PHC) but represents a unique brain region to the PHC. Thus, a direct translation of AT1 receptor localisation from parts of the rodent parahippocampal region to the human PHC remains inconclusive.

In particular, more recent rodent studies discuss whether the 'postrhinal' cortex within the rodent parahippocampal region might serve as a more precise functional homologue to the human PHC (Estela-Pro & Burwell, 2022). However, the terminology and anatomical distinction between 'parahippocampal region' 'entorhinal cortex' and 'postrhinal cortex' was not well established at the time, when the studies on AT1 receptor localisation were conducted in the 1990s (for discussion, see Burwell et al., 1995; von Bohlen und Halbach & Albrecht, 1998). Thus, it remains unclear whether (i) these studies looked at the whole parahippocampal region and only observed receptors in the entorhinal cortex, or whether (ii) they used the term 'entorhinal cortex' to refer to wider tissues adjacent to the hippocampus (e.g. also including postrhinal cortex), or whether (iii) they investigated the entorhinal cortex only. Notably, the distribution of AT1 receptors in the brain

remains consistent among various mammalian species (Allen et al., 1998), making a general translation from rodents to humans possible.

Nevertheless, AT1 receptor expression in the human brain has been confirmed in hippocampus and entorhinal cortex in the 1990s (Barnes et al., 1993), but it is unclear whether the PHC has been investigated.

Taken together, it proves challenging to directly confirm or disprove AT1 receptors in the human PHC based on previous research only. Future studies on postmortem brain tissue secretion are required to draw a final conclusion.

Overall, since AT1 receptor expression has not been confirmed in the PHC (yet), it may be possible that ARBs only indirectly modulate PHC activity. For instance, ARBs may modulate hippocampus functioning on a small scale which is too granular to be detected by fMRI. Yet, such potential hippocampal modulation may lead to changes in PHC activity through interconnections between the hippocampus and PHC.

6.3.3. Understanding the Lack of ARB Effects on the Hippocampus and Memory Performance

In this thesis, there was no ARB effect on memory performance nor the hippocampus during memory formation, despite a broad body of work has suggested an ARB involvement in improving memory and a modulatory role on hippocampal functioning (Bild et al., 2013; Drews et al., 2021; Fogari et al., 2003; Fogari et al., 2006). However, since memory formation is a highly complex cognitive process, there are multiple factors that could explain the absence of effects in this DPhil research.

Firstly, the episodic memory task was relatively elementary. It consisted of a block design of 'familiar' images which had previously been encoded, and 'novel' images which remained to be encoded. The direct comparison of the two conditions (novel > familiar) should represent memory encoding.

However, this task does not allow to investigate 'successful' memory encoding, as not all novel images will be remembered correctly but some will be forgotten. Thus, brain activity during encoding of novel images may be confounded by items which will be forgotten later. In future studies, an event-related memory task is necessary to obtain a more fine-graded differentiation between remembered and forgotten items. In fact, neurocognitive research on memory formation widely applies such event-related designs (e.g. Davis et al., 2021; Dickie et al., 2008; Erk et al., 2003; Fletcher et al., 2003; Park et al., 2013). In addition, the event-related approach would also allow to use PSA on an item level, which may yield more fine-graded results on voxel activity pattern stability during memory encoding (Ritchey et al., 2013).

One of the reasons for the absence of ARB effects on behavioural memory performance may be the timing of the recognition test, which was conducted 1hr after memory encoding and may have been too early. Potentially, ARBs modulate memory consolidation or long-term memory performance which would require a more delayed recognition test, for instance on the next day. This would be in line with rodent work on fear extinction, which showed a delayed effect of ARBs. That is, ARB-treated (vs vehicle) animals showed a reduced fear response when exposed to the threat cue the following day, but no difference in response during the actual fear extinction training (Marvar et al., 2014; Parrish et al., 2019). Potentially, the same is true with ARB induced effects on memory performance becoming evident after a delay.

Thirdly, losartan may restore *dysfunctional* memory formation, but not further enhance already intact memory formation. In support, memory enhancing effects of ARBs have been shown in elderly participants, who likely show impairments in memory performance compared to younger adults recruited for this DPhil research (Fogari et al., 2003; Fogari et al., 2006). Similarly, ARB administration in rodents restored memory function after being experimentally impaired via stress (Braszko et al., 2013;

Wincewicz et al., 2016) or in Alzheimer's disease models (Drews et al., 2021). This would align with rodent studies on fear extinction, which showed that ARBs did not improve fear extinction generally (Parrish et al., 2019; Quiñones et al., 2016), but only in those animals in which extinction deficits were experimentally induced via lipopolysaccharide injection (Quiñones et al., 2016), oestradiol downregulation (Parrish et al., 2019) or MAS-receptor deletion (Lazaroni et al., 2016). While requiring memory dysfunctions to observe ARB effects on memory performance would not be a direct concern for PTSD research in clinical populations, it proves a major challenge for pre-clinical and analogue research as participants are likely to be healthy and not show deficient memory performance. As a very first step, future studies could increase task difficulty for participants to achieve less accuracy to resemble memory dysfunctions. However, increased task difficulty may only partially translate to the neural mechanisms underlying impaired memory function in PTSD.

In addition, the lack of ARB-induced hippocampus and behavioural memory effects may indicate that ARBs do not influence memory formation or hippocampal functioning for neutral events. Instead, the modulatory role of ARBs may only become evident in emotional memory paradigms or interactions between the hippocampus and limbic structures. This is in line with initial evidence on healthy participants showing that ARBs reduced memory performance for negative events and reduced hippocampus-amygdala coupling (Xu et al., 2022). Hence, it is necessary to continue investigating ARBs effects on stimuli with different emotional valence.

6.3.4. Reassessing the Role of ARBs on Hippocampal Processing – Implications for Task Selection

Ultimately, hippocampal functioning extends beyond memory formation. Thus, it is plausible that ARBs modulate hippocampal functioning but not memory formation, which would imply using a different paradigm to probe

hippocampal functioning. For instance, rodent work has shown that ARBs modulate different markers of hippocampal plasticity, such as hippocampal neurogenesis (Drews et al., 2021), long-term potentiation (LTP) (Hosseini et al., 2021) or expression of the brain-derived-neurotrophic factor (BDNF) (Wincewicz et al., 2016). In turn, aberrations in hippocampal plasticity are currently being discussed as a transdiagnostic mechanism and novel therapeutic target in psychiatric disease (DeCarolis & Eisch, 2010; Jun et al., 2012; Senter et al., 2016). However, studies on hippocampal plasticity are difficult to establish in human research, as direct measures would require assessments at a synaptic or cellular level.

So far, innovative brain imaging approaches have been developed to take a step towards assessing hippocampal plasticity. For instance, functional magnetic resonance spectroscopy (fMRS) during an associative learning paradigm has sensitively captured rapid changes in hippocampal glutamate levels as a marker of synaptic plasticity (Stanley et al., 2017). In addition, a diffusion tensor imaging paradigm involving a spatial learning and memory task has been shown to detect rapid white matter changes in the hippocampus and PHC (Sagi et al., 2012).

On the other hand, a more indirect measure of human hippocampal plasticity may be the measurement of neurotrophic factors like BDNF and fibroblast-growth factor II (FGF2) in serum or plasma. BDNF and FGF2 play a key role in basic neuronal mechanisms such as cell proliferation, migration and differentiation (for recent reviews, see Klimaschewski & Claus, 2021; Kowiański et al., 2018). In fact, they have been implicated in hippocampal neurogenesis (Mudò et al., 2009) and more recently also in psychiatric disease (Anita & Lisa, 2012; Notaras & van den Buuse, 2020; Turner et al., 2011; Turner et al., 2016; Zou et al., 2024). Notably, there is initial evidence that ARBs can upregulate BDNF expression (Alhusban et al., 2013; Goel et al., 2018; Ping et al., 2014; Wincewicz et al., 2016), although not unequivocally confirmed (Salmani et al., 2020).

A more behavioural proxy for neuroplasticity and hippocampal functioning may involve the use of a pattern separation task. Pattern separation is referred to the neurocognitive process of distinguishing between similar experiences and memories (Yassa & Stark, 2011). It reflects the brain's ability to store events that occur in similar contexts or have overlapping elements into distinct memory representations (Yassa & Stark, 2011). While there is increasing evidence from animal studies that pattern separation may actually be underpinned by hippocampal neurogenesis (Clelland et al., 2009; França et al., 2017), impaired pattern separation has been implicated in fear generalisation (Lange et al., 2017), childhood adversity (Lecei & van Winkel, 2020) and contextual fear learning (Neudert et al., 2023) .

In PTSD, the adoption of the pattern separation task may be particularly relevant for two reasons: First, PTSD development is characterised by a dysfunctional integration of the traumatic experience into the episodic memory system (e.g. Brewin, 2014). Second, PTSD patients show an impaired differentiation between threat and safety cues (e.g. Jovanovic et al., 2012). Thus, PTSD-related neurocognitive processing may include fundamental impairments to create distinct memory representations of events which are perceptually similar yet conceptually different (e.g. when encountering a perceptually similar cue to those encountered during trauma, but in a safe context).

Taken together, although no ARB effects in memory formation and hippocampal functioning have been shown in this thesis' episodic memory task, it remains unknown to what extend the lack of effects may have been influenced by the selection of the experimental paradigm. Thus, it is important to look at task-independent approaches such as resting state functional connectivity.

6.3.5. Overcoming Task-Based Limitations – Insights from Resting State

To overcome limitations of precise task selection in functional imaging studies, resting state functional connectivity analyses have become an increasingly popular tool in clinical research, which was also employed in this thesis.

While there was no effect of losartan on hippocampus task-based mean activity or stability in this DPhil research, the resting state functional connectivity (rsFC) analysis showed that losartan effects included hippocampal modulation. This may indicate that losartan does not directly modulate hippocampal mean activity or stability, but rather affects its functional connectivity to other brain areas. This would be in line with previous research showing that hippocampus-amygdala coupling was reduced during emotional memory formation (Xu et al., 2022). In addition, it may indicate that ARBs indeed influence hippocampal functioning, but the chosen episodic memory task was not suitable to capture these effects as discussed in the previous paragraph.

More specifically, our results showed that a single dose of losartan reduced hippocampus and inferior frontal gyrus (IFG) coupling. This is particularly important, as increased hippocampus-IFG coupling has been reported in PTSD patients (Sheynin et al., 2020). Indeed, the IFG has been implicated in memory intrusion development in trauma analogue studies using the trauma-film paradigm (Bourne et al., 2013; Clark et al., 2016). Thus, we present preliminary evidence that ARBs may be able to reverse such functional connectivity effect, which may speculatively lead to reduced development of memory intrusions.

Since the IFG is part of the salience network (Seeley et al., 2007), our results could further be interpreted that ARBs reduce the influence of emotional valence on memory formation. Notably, in the data-driven ICA there was no

effect on the identified salience network, so that this interpretation needs to be treated with caution and warrants further investigation and replication.

In addition to the reduced rsFC between hippocampus and IFG, our results show that losartan reduced rsFC between the PHC and DLPFC, which is part of the frontoparietal network (Seeley et al., 2007). This result has not previously been reported yet and may seem counterintuitive as increased connectivity between the DLPFC and regions in the medial temporal lobe (such as the PHC) have been implicated in successful memory formation (Leshikar et al., 2017). However, given that previous work has shown that ARBs facilitate visual processing (Shkreli et al., 2020) and that this thesis showed that ARBs modulate PHC functioning, we cautiously speculate that the decreased coupling between the PHC and DLPFC may be interpret as a decreased coupling of higher-order visual processing mechanisms from their top-down control. As a result, this may preserve the visual complexity of the stimuli leading to more in-depth perceptual integration into the autobiographical memory system. However, while this interpretation remains merely speculative, our results continue to underline the importance of directly addressing PHC functioning in future ARB research.

Interestingly, the current resting state results highlight that ARB effects were only present in the memory system seeds, rather than anxiety seeds (amygdala, anterior insula), which highlights the relevance to continue investigating the hippocampus, PHC and memory formation in central ARB action.

Notably, this does not disregard the importance of examining anxiety-relevant neurocognitive domains, especially due to the well-documented anxiolytic effects (e.g. de los Angeles Marinzalda et al., 2014; Llano López et al., 2012; Ping et al., 2014). Rather, it advocates for extending research into the broader spectrum of central ARB action to advance a holistic understanding.

6.4. Implications of the Stress Study Results

Moving towards a holistic understanding of PTSD-relevant ARB action, another domain which remains to be more thoroughly investigated in humans is the stress response, which has been the focus of the final data chapter in this thesis (chapter *5*).

Stress is an important modulator of neurocognitive processing, while maladaptive stress responses have been implicated as a transdiagnostic process in psychiatric disease with a particular emphasis in PTSD pathogenesis (Goodman et al., 2012; Pitman et al., 2012). To date, animal models have shown that ARBs reduce HPA-axis and SNS stress responses (Armando et al., 2001; Armando et al., 2007; Pavel et al., 2008) and restore stress-induced impairments in learning and memory (Braszko et al., 2013; Wincewicz et al., 2016). Similarly, previous research in our group showed that a single dose of losartan (vs placebo) reduced HR and the LF/HF ratio of HRV during distressing film clip presentation (Shkreli et al., 2020). Yet, this thesis shows that there were no ARB effects in response to performance stress, while exploratory analyses showed that ARB administration may restore a blunted cortisol response in hormonal contraception users.

This sub-chapter begins with a discussion on whether potential ARB effects on the human stress response require higher stress levels or a different choice of stressor. It continues with a discussion on oestrogen modulation of RAS activity with particular focus on the role of hormonal contraceptives, followed by discussing sex effects in ARBs action more broadly including potential implications for future ARB research.

6.4.1. No ARB Effects on Performance Stress – Does the Stressor Matter?

Although previous work in our group has shown that ARBs reduced HR and the LF/HF ratio of HRV during stress exposure using the trauma film

paradigm (Shkreli et al., 2020), we could not replicate these findings using a performance stress task in this DPhil research. In fact, ARBs did not show any effect on any of the examined stress markers, including salivary cortisol response and subjective stress ratings. Notably, the performance stress paradigm in this thesis appeared to be less stressful compared to the trauma film paradigm used in our previous study (Shkreli et al., 2020). To illustrate, both studies measured HR and the LF/HF ratio of the HRV. While in our previous research HR rose from 70 to 90 in the placebo group during trauma film presentation, in the current study it rose from 66 to 69 in the placebo group during the performance stress paradigm. In addition, the performance stress task did not lead to an increase in the LF/HF ratio of HRV– which is a marker of SNS involvement (Rajendra Acharya et al., 2006). This indicates that even across groups the task did not induce an SNS stress response responsible for the 'fight or flight' reaction, in contrast to the trauma film study.

The performance stress paradigm was employed in this DPhil research as it was based on the most popular stress paradigm in human research – the TSST (Kirschbaum et al., 1993) – without needing human actors to be administered. However, the social evaluation component, which is crucial in the TSST, is lacking in the performance stress paradigm. In addition, most participants correctly guessed the stress deception. Thus, the performance stress paradigm may have not led to the desired levels of stress, which may have limited potential ARB effects.

In addition, the performance stress paradigm may have been too unrelated to traumatic stress, potentially explaining the lack of ARB effects. Traumatic stress is characterized by perceived threat, unpredictability and uncontrollability (Foa et al., 1989). These characteristics are not reflected well by performance stress, which includes a highly cognitive component and may be more closely related to common stressors instead, for instance taking an exam. Thus, it is possible that the perceived threat and anxiety

component, which is absent during performance stress, is the key modulator of ARB action on the stress response.

Overall, chapter 5 highlights that ARB effects on the stress response may not universally translate to different stressors, in which the use of a performance stress paradigm may have not been the most suitable.

In contrast to a lack of SNS stress response, the performance stress paradigm increased the cortisol response across groups. Although there were no effects of ARB intake on the cortisol response in our main analysis, our exploratory results showed that losartan restored the blunted stress response of hormonal contraception users. This is particularly interesting, as altered cortisol secretion in hormonal contraceptive users was suggested to resemble those of individuals exposed to chronic stress (Hertel et al., 2017). Apart from hormonal contraception, a blunted cortisol response has been associated with greater lifetime stress and PTSD diagnosis, respectively (Lam et al., 2019; Metz et al., 2020). Thus, it may be plausible that the effects of ARBs on the cortisol response only become evident during chronic stress exposure, in which ARB administration may preserve a functional cortisol response to (chronic) stress. Notably, this interpretation implies that potential ARB effects in restoring a blunted cortisol response translate beyond hormonal contraception intake, which warrants targeted investigation.

Mechanistically, the interaction effect between ARBs and hormonal contraception intake may be underpinned by interaction effects between the RAS and oestrogen, with potentially far-reaching implications for future ARB research. Yet, the direct mechanistic pathways remain to be established.

6.4.2. The role of Oestrogens and Hormonal Contraceptives in the RAS

There is strong evidence for sex differences in RAS activity, primarily modulated by sex hormones such as oestrogens, which may underlie sex differences in cardiovascular disease (Hilliard et al., 2013; Komukai et al., 2010). Oestrogens are a group of gonadal hormones consisting of oestradiol – the most potent and prevalent form in women of reproductive age – as well as estrone and estriol (Weichman & Notides, 1980).

The influence of oestrogens on the RAS is multifaceted. For instance, oestrogens can downregulate renin release which is the enzyme initiating the RAS cascade (Hilliard et al., 2013; Komukai et al., 2010). On the other hand, oestrogens can upregulate angiotensinogen release (Hilliard et al., 2013), which is a precursor of angiotensin-II. Adding to the complexity, oestrogen modulates angiotensin-II AT1 and AT2 receptor balance via downregulating AT1 receptor expression and upregulating AT2 receptor expression (Hilliard et al., 2013; Macova et al., 2008; O'Donnell et al., 2014; Suarez et al., 2004). As a result, the ability for AT2 receptors to bind angiotensin-II is enhanced. Importantly, AT2 receptors have neuroprotective properties counteracting AT1 receptor signalling, which is responsible for the typical angiotensin-II mediated effects like vasoconstriction or the pro-inflammatory response (Hernandez Schulman et al., 2007).

In fact, it has been shown that the oestrogen-induced shift of angiotensin-II signalling to AT2 receptors results in opposite effects between sexes: while the administration of low doses angiotensin-II reduced blood pressure in female rats, blood pressure in male rats was elevated (Sampson et al., 2011; Sampson et al., 2008). Overall, although the modulatory role of oestrogen on the RAS is complex, it predominantly seems to contribute to the system's downregulation (Ashraf & Vongpatanasin, 2006).

Despite the downregulating influence of oestrogens on the RAS, hormonal contraceptives have been repeatedly associated with upregulated RAS activity and elevated angiotensin-II levels (Kang et al., 2001), although the exact underlying mechanisms remain unclear (Ashraf & Vongpatanasin, 2006). Since hormonal contraceptives not only contain synthetic oestradiol but also the synthetic progesterone 'progestin', their complex interplay may be responsible for a RAS upregulation (Ashraf & Vongpatanasin, 2006). On the other hand, exogenous administration of oestradiol through hormonal contraception suppresses oestrogen synthesis in the ovaries (Rivera et al., 1999). As a result, circulating oestrogen levels are attenuated to a point resembling the low-oestrogen phase of the menstrual cycle (Pluchino et al., 2009), which may attenuate the protective effects of circulating oestrogens on the RAS. This idea suggesting that the protective impact of circulating oestrogen is reduced, is based on similar effects proposed in the context of hormonal contraceptive intake impairing fear extinction (Graham & Milad, 2013).

Notably, animal studies provide initial evidence that ARBs can restore deficits in fear-extinction and cognition caused by low-oestradiol state induced by hormonal contraception administration or ovariectomy (Campos et al., 2020; Parrish et al., 2019).

Since hormonal contraception intake modulated peripheral angiotensin-II signalling (Kang et al., 2001), it is possible that central ARB effects may also be modulated by hormonal contraceptives more generally. Therefore, in future ARB studies, it is important to systematically assess hormonal contraception intake and explore whether hormonal contraceptives indeed modulate central ARB action on a behavioural and/or neural level.

6.4.2. Considering Sex Differences in ARB Research

Given the strong modulatory role of oestrogens on the RAS, it is likely that sex effects are present in ARB action. In fact, previous research has demonstrated that ARB efficacy in regulating blood pressure differs between men and women (Miller et al., 2006). Similarly, low doses of angiotensin-II administration exhibited opposite effects between male and female rodents which was suggestibly mediated by oestrogen levels. That is, blood pressure in male rodents was elevated, while blood pressure in female rodents was attenuated after low-dose angiotensin-II administration (Sampson et al., 2011; Sampson et al., 2008). However, sex effects in central ARB action, especially relevant to psychiatric conditions, have not been explicitly investigated.

In contrast, some of the previous studies in fear extinction (Zhou et al., 2019) and emotional memory (Xu et al., 2022) have exclusively recruited male participants. Similarly, most animal studies on ARB action have been conducted in male rodents (e.g. Llano López et al., 2012; Marvar et al., 2014; Ping et al., 2014; Wincewicz & Braszko, 2014a; Wincewicz et al., 2016). Thus, such findings of central ARB action cannot, in a very strict sense, be fully generalised to women considering ARBs likely underlie sex effects (Miller et al., 2006).

It remains somewhat unclear why predominantly male samples have been examined in studies aiming to elucidate mechanisms underlying anxiety and PTSD development. The reasoning includes that fluctuating oestrogen levels in women are seen as a confounding factor for ARB effects (Xu et al., 2022). However, women are more than twice as likely affected by anxiety disorders and PTSD (Kilpatrick et al., 2013; McLean et al., 2011), which can only be partially explained by environmental factors like trauma type and traumatisation at younger age in women (Ramikie & Ressler, 2018). Neurocognitive mechanisms including fear processing and sex hormone modulation seem to play an additional crucial role (for reviews, see Kornfield

et al., 2018; Li & Graham, 2017; Ramikie & Ressler, 2018). Thus, it remains to extend and replicate previous findings on central ARB action in a female – or at least gender-balanced – sample to ensure clinical applicability in the future.

Accordingly, this DPhil research primarily recruited female participants (memory study: 82.5% female, resting state study 73.3% female, stress study 62.5% female), which more closely aligns to the gender distribution in anxiety disorders and PTSD. Nevertheless, to improve the mechanistic understanding of neurocognitive ARB action, future studies should adequately power to directly test for sex effects and assess menstrual cycle status in women.

6.5. Summary: Implications of Current ARB Effects in PTSD

Figure 6.1. summarises how the results from this DPhil research extend previous work on central ARB action relevant to PTSD.

Overall, this thesis underscores the role of ARBs in neurocognitive processing relevant to PTSD extending beyond effects on anxiety, fear extinction, and reward learning. It demonstrates that ARBs act on the intersection of higher-order visual processing and memory formation, with a notable involvement of the PHC in all fMRI chapters.

The PHC represents the intersection of visual processing and memory, while aberrations in the integration of visual cues into the episodic memory system have been linked to memory intrusions (Ehlers & Clark, 2000). Similarly, IFG activity has been linked to memory intrusions in trauma-analogue studies (Bourne et al., 2013; Clark et al., 2016). Therefore, one mechanism through which ARBs may contribute to PTSD prevention may involve improving the visual integration of trauma-specific cues into episodic memory preventing intrusion development – through activity

differences in the PHC, and through reducing functional connectivity between the hippocampus and IFG. However, at this point, such proposed mechanism remains speculative, particularly since this DPhil research did not directly investigate memory intrusions.

While the results on ARB facilitating PHC processing are in line with preliminary evidence showing that ARBs improve visual processing of negative material (Shkreli et al., 2020), no significant effects were observed on overall memory performance.

Looking at the bigger picture, previous work showed that a single dose of ARBs reduced memory for negative images (Xu et al., 2022) and increased learning from appetitive compared to aversive material (Pulcu et al., 2019). In addition, the neuroimaging results in this thesis support a role of ARBs on the memory network, while there were no behavioural effects in memory performance using neutral material. Together, this may suggest that future research should continue to focus on interactions between cognition and emotion to obtain a more nuanced understanding of central ARB action. This idea is further supported by the resting-state chapter, which indicates that ARBs decrease coupling between the hippocampus and the Inferior Frontal Gyrus (IFG) of the salience network.

In addition, no ARB effects were observed in response to performance stress. This contrasts previous work showing stress-reducing effects of ARBs in animal models (Armando et al., 2001; Armando et al., 2007; Pavel et al., 2008; Wincewicz et al., 2016), and reduced SNS activity during distressing film exposure in humans (Shkreli et al., 2020).

Therefore, it becomes evident that the modulatory effects of ARBs on the stress response are more nuanced than initially assumed. This thesis highlights that the effects of ARBs on stress cannot be universally translated across different stressors. On the one hand, it is plausible that the stressor itself has been too mild and not sufficiently relevant, given that most

participants guessed the stress deception. Similarly, the current results raise the question, whether ARBs may only modulate the SNS stress response which was not pronounced in the performance stress task here, but has been shown in our previous research (Shkreli et al., 2020). On the other hand, ARB action on the stress response may require a component of fear and anxiety, which is lacking during performance stress, making it difficult to compare the current results to our previously published study with the trauma film paradigm (Shkreli et al., 2020).

Furthermore, the current results raise the question whether ARBs may have more of a 'restoration' rather than a general enhancing effect on neurocognitive processing, which would be in line with animal research showing that ARBs restored fear extinction deficits (Lazaroni et al., 2016; Parrish et al., 2019; Quiñones et al., 2016) and stress-induced cognitive impairments (Lazaroni et al., 2012; Wincewicz & Braszko, 2014a, 2014b; Wincewicz et al., 2016). For instance, in chapter 5 it was shown that ARBs restored the blunted stress response in hormonal contraception users, while not modulating cortisol response generally. On the other hand, this idea may partially explain the lack of behavioural effects on memory performance and hippocampal processing in the memory study, since participants were showing healthy/normative memory responses.

Overall, rather than answering mechanistic questions of ARB action, this thesis contributed to opening up more avenues for future research. In particular, it is difficult to establish a mechanistic pathway of ARB action without clear behavioural results. Although the discussion on the current results is based on mechanistic frameworks of PTSD pathogenesis alongside previous work on central ARB action, the proposed mechanisms cannot be confirmed or disproved without behavioural proxies and future studies. Thus, this thesis should be taken as a first step for more targeted research, while its results propose to focus on ARB effects on PTSD-related visual processing and PHC function.

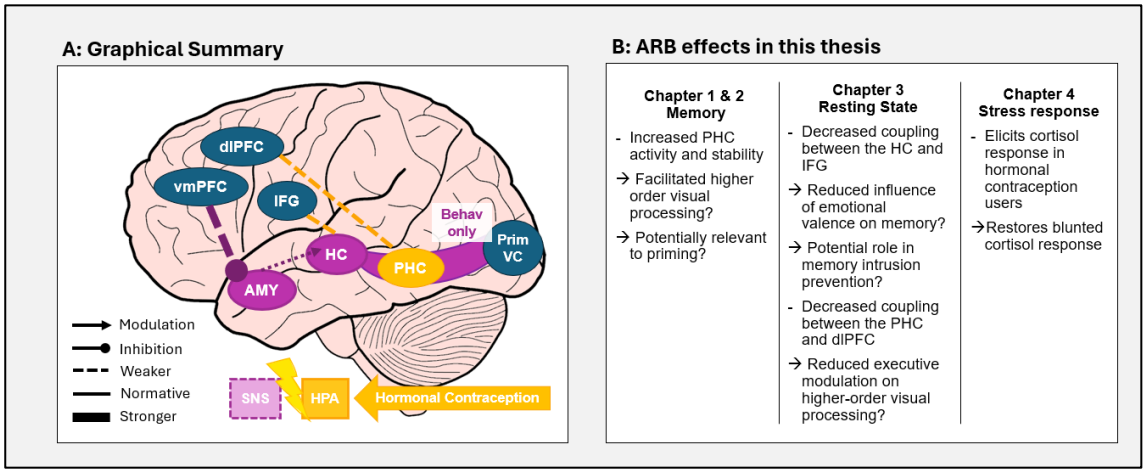


Figure 6.1. Integration of the current results into the ARB literature. A: purple colour indicates ARB effects which have been shown in previous research (see figure 1.5. in the introduction). Yellow colour highlights where this thesis expands previous work. B: Written outline of the key results in this thesis.

6.6. Moving Forward towards Mechanistic Understanding of ARB Action

While the previous sub-chapters have focused on the interpretation and the implications of the results in this thesis, the following sub-chapter takes a step further. It discusses the next steps which are required to gain a mechanistic understanding of central ARB action in PTSD – starting with one of the key questions in neurocognitive ARB research, namely which angiotensin metabolite is responsible for central ARB effects. It is followed by discussing general challenges in establishing a mechanistic pathway and the importance of an interdisciplinary approach. This sub-chapter ends with a critical discussion on whether a full mechanistic insight is necessary to initiate clinical applicability.

6.6.1. The Big Unknown – Does ARB Action Require Angiotensin II or Angiotensin IV Mediated Pathways?

In general, the understanding of ARB effects in psychiatric disease is very limited. Although there are population-based studies showing protective effects of ARBs in PTSD symptom development (Khoury et al., 2012; Seligowski et al., 2021), they do not acknowledge underlying mechanisms.

Even within the rodent literature the mechanistic pathway of ARB action in memory and cognition is not fully understood. One of the most essential questions is, which receptors are involved in mediating central ARB effects. This may sound surprising as ARBs primarily bind to AT1 receptors. However, there is ongoing debate, whether AT1/AT2 receptor action mediates the beneficial effects of ARBs in cognition – particularly in memory – or whether these positive effects are attributable to angiotensin-IV action instead.

It has been proposed, that due to AT1 receptor blockade (by ARBs like losartan), there is more free angiotensin-II to be subsequently converted to angiotensin-IV, which then exerts the proposed effects on cognition (Gard, 2008; Wright & Harding, 2013; Wright et al., 2008). Indeed, it has been recently shown in human postmortem brains that ARB use was associated with increased angiotensin-IV receptor expression (Cosardereliogl u et al., 2022) and there is preliminary rodent work confirming that losartan-induced memory improvements were mediated by angiotensin-IV receptors in an Alzheimer model (Royea et al., 2017). Many potential neurobiological mechanisms have been suggested to underlie angiotensin-IV mediated effects on memory and cognition, albeit not yet proven (for detailed discussion, see Gard, 2008; von Bohlen und Halbach, 2003; Wright & Harding, 2011; Wright et al., 2008). In particular, it is still under debate whether angiotensin-IV receptors are insulin-regulated aminopeptidase (IRAP) receptors (Albiston et al., 2001; Albiston et al., 2003; Gard, 2008), or c-Met receptors (Wright et al., 2008). For example, IRAP receptor mediated

mechanisms of angiotensin-IV action were suggested to rely on elevated glucose uptake in the brain, enhanced hippocampal long-term potentiation (LTP) and enhanced hippocampal acetylcholine release. On the other hand, c-Met receptor mediated mechanisms were suggested to rely on increased hippocampal LTP and NMDA receptor augmentation. Newer reports further suggest that angiotensin-IV might work through protein kinase Mzeta (PKMzeta) activity (Chow et al., 2015), which is suggested to play a crucial role in long-term memory through the maintenance of LTP, although the exact underlying pathway remains to be fully understood (Patel & Zamani, 2021). While the proposed mechanism of angiotensin-IV action generally share a modulatory role on LTP, no clear receptor-mediated pathway has been proven yet. Further, the state of the literature is too sparse to confirm angiotensin-IV receptor action after ARB administration in general, albeit proposed. Hence, any results should be merely interpreted based on angiotensin-II and AT1 mediated effects in memory and cognition for now, such as reductions in oxidative stress (Bild et al., 2013), anti-inflammatory properties (Salmani et al., 2020) – and enhancements in hippocampal LTP (Hosseini et al., 2021).

6.6.2. The Importance of an Interdisciplinary Approach

One of the key challenges in establishing a mechanistic pathway from receptor-mediated ARB effects to clinical outcomes in PTSD symptom prevention is that there are two major lines of evidence:

On the one hand, there are population-based studies showing protective effects of ARBs in PTSD symptom development (Khoury et al., 2012; Seligowski et al., 2021). On the other hand, most experimental studies have focused on animal models to gain a mechanistic understanding of central ARB action which is yet too selective to be translated into clinical applications (e.g. Hosseini et al., 2021; Marvar et al., 2014; Salmani et al.,

2020; Wincewicz et al., 2016). Yet, there is only limited knowledge between those two ends, which is required to move forward.

Taking a step towards bridging this gap, this DPhil research lies somewhere in between. By using neuroimaging and biological markers, this DPhil research aims to advance a more mechanistic understanding of ARB action in PTSD development with a neurocognitive focus on memory and the human stress response.

However, to effectively develop ARB-mediated neurobiological pathways more generally, it is crucial to adopt an interdisciplinary research approach. To illustrate, it is difficult to translate complex neurocognitive processes in humans to precise receptor-mediated effects, particularly since there is limited knowledge on the role of AT1 receptors in psychiatric disease. On the other hand, rodent studies can provide valuable insights into precise receptors mediated effects, but are not capable to capture the multifaceted components of human cognition and psychiatric disease. Thus, even if an exact receptor mediated pathway is established in rodents, it remains to be investigated how such proposed pathway extends to human cognition and clinical outcomes.

From a pragmatic perspective, animal models testing both sexes are needed to guide the direction of human research, which subsequently aims to translate findings into a neurocognitive context – again testing both sexes.

In this regard, it is important to integrate methods from basic human neurosciences with clinical knowledge to ensure that research moves forward most efficiently. While basic neurosciences methods allow for a more fine-graded understanding of the neural underpinnings of ARB action, clinical research is necessary to guide study objectives into clinically relevant questions. Thus, an interdisciplinary approach is necessary to move forward and to ultimately inform a clinical application.

6.6.3. Practicability versus Understandability

To progress with clinical application, it is not only important to understand ARBs' mechanistic pathways, but also to what extent such understanding is necessary to improve patient care. This discussion inherently involves a cost-benefit consideration, in which additional research costs (e.g. time, ethical considerations, financial resources) are weighted against the incremental benefits gained from a deeper mechanistic understanding. To illustrate, the mechanisms of paracetamol are not fully understood despite its longstanding use for pain and fever (for review, see Ayoub, 2021). An example in psychiatry are neuroleptics, whose clinical utility for managing psychosis was recognized before elucidating their dopaminergic mechanisms (Cunningham Owens & Johnstone, 2018). These examples highlight the pragmatic aspect of clinical research in which meaningful advancements can be achieved without a priori mechanistic knowledge.

With regards to ARBs, an RCT in outpatients with PTSD has been recently conducted which did not show any therapeutic effects on PTSD symptoms compared to placebo (Stein et al., 2021). In this study, patients were either prescribed 10-week losartan administration or equivalent placebo. Their PTSD symptoms were assessed several times across study participation via psychiatric interview by a trained psychologist. However, ARBs (vs placebo) were given as a sole treatment to patients without any complementing psychological or pharmacological interventions. This approach was chosen to align with the population-based studies showing an association between ARB intake and reduced PTSD symptom development which did not consider any additional preventative component or active ingredient. However, there is a distinction between prevention and intervention from a clinical perspective. Given that previous research has shown that ARBs improved fear extinction (Marvar et al., 2014; Zhou et al., 2019), a more suitable translation to clinical settings would include to administer ARBs to

patients with PTSD in addition to their psychological treatment, which ideally includes elements of exposure therapy.

This RCT clearly illustrates the importance of establishing a mechanistic understanding prior to clinical application. On the other hand, it is inefficient to dedicate extensive periods to unravelling every detail of a mechanistic pathway prior to its clinical translation. To illustrate, although animal models or cell cultures provide precise mechanistic insights, they cannot capture the cognitive elements of PTSD, the full spectrum of PTSD symptoms, nor the environmental influences. Adding to the complexity, patients with PTSD are regularly diagnosed with medical and psychiatric comorbidities and take medication.

Taken together, a collaborative and parallel effort across disciplines including animal, cellular and human research is required to reciprocally inform one another, while it is crucial to balance mechanistic discovery and clinical application.

6.7. Practical Considerations for Future ARB Research

In the last sub-chapter of this thesis, the following paragraphs include some practical considerations to guide future neurocognitive research of central ARB action and their potential clinical implications for PTSD.

6.7.1. Optimizing ARB Selection and Intake Duration

To date, various ARBs (e.g. losartan, telmisartan, candesartan, valsartan) have been utilized interchangeably in research studies, notwithstanding their distinctive metabolic profiles. The most widely studied ARB has been losartan within both rodent models and human research. Given that drug peak levels are reached within one hour (Lo et al., 1995; Ohtawa et al., 1993), it is highly suitable for experimental studies investigating immediate ARB effects. However, different ARBs may be more suitable for neurocognitive

research which warrants further exploration. For instance, candesartan and telmisartan exhibit a higher affinity to AT1 receptors (Fabiani et al., 2000; Oparil, 2000; Vanderheyden et al., 1999) and demonstrate enhanced efficacy in crossing the blood-brain barrier (Noda et al., 2012; Villapol & Saavedra, 2015). However, candesartan reaches its drug peak level after 3 to 4 hours, making it less practical for single-dose studies in experimental settings. On the other hand, telmisartan is recognised as the ARB to cross blood-brain barrier most effectively due to its pronounced lipophilicity (Michel et al., 2013), while the peak levels are reached within 1 hour of administration, highlighting telmisartan as a promising candidate for central-acting ARB research and may suggest a shift towards its increased use in human ARB studies.

In addition, not only the choice of the ARB, but also the choice of its dosage and duration is important to consider in future research. For instance, a wide body of animal studies on central ARB effects, have used prolonged ARB administration of several days up to 4 weeks (e.g. Braszko et al., 2013; Ping et al., 2014; Wincewicz et al., 2016), or have injected acute doses directly into the brain (de los Angeles Marinzalda et al., 2014; Llano López et al., 2012). Thus, higher levels of ARBs were present in the brain during experimental testing. Similarly, the population-based studies examined people who were prescribed regular ARBs to treat hypertension (Khoury et al., 2012; Seligowski et al., 2021), suggesting that a prolonged administration may be necessary to exhibit preventative effects on PTSD symptoms.

Conversely, experimental human work almost exclusively used a single ARB dose (Pulcu et al., 2019; Shkreli et al., 2020; Xu et al., 2022; Zhou et al., 2019; Zika et al.). Hence, it remains unclear whether prolonged administration is required to observe more pronounced effects. Particularly in case of null-results, it is unknown whether ARBs generally do not have an effect on the neurocognitive process in question, or if a higher dosage is required to observe the suggested effects. Taken together, investigating prolonged ARB

administration is an important next step in human research, to maximise effects.

Recruiting participants who routinely take ARBs for hypertension treatment might pose challenges due to their likely older age and possible medical comorbidities, which may bias potential effects on PTSD-relevant cognitive processing. Notably, an initial study has administered low doses of losartan for 10 consecutive weeks to physically healthy, normotensive PTSD patients, without noticeable side effects (Stein et al., 2021). Thus, future studies may include prolonged ARB administration in healthy volunteers after consultation with a medical doctor.

6.7.2. Challenges in Selecting Study Populations in PTSD Research

Establishing a suitable study population in pre-clinical research on PTSD remains challenging. While in this thesis three data chapters included high trait anxiety participants as a first step to initiate PTSD applicability, it is important to note that this does not equate to PTSD, highlighting a limitation of this approach.

By recruiting high trait anxiety participants, clinical applicability is initiated without collaterally inducing stress (i.e. by showing distressing film material to induce trauma-analogue experiences). In the latter case, any potential ARB effects on cognition would likely be confounded with stress effects due to trauma film presentation. On the other hand, recruiting normative anxious volunteers would offer even more limited insights into PTSD applicability.

Rather than participants scoring higher on trait anxiety, future studies may wish to recruit healthy volunteers above a certain score on the childhood trauma questionnaire (Scher et al., 2001). Similarly, future studies may wish to recruit participants who have experienced a traumatic event but did not develop PTSD. However, while these samples would more accurately reflect direct trauma exposure, it poses the risk of including participants resilient to

PTSD (since they were exposed to trauma but remained healthy), which may bias results on ARB effects.

For more targeted and clinically relevant insights, recruiting participants from settings like emergency rooms, areas of high conflict, or among patients diagnosed with PTSD would be ideal. However, the vulnerability of these populations and the substantial resources required for such recruitment underscore the necessity of first identifying potential mechanisms in pre-clinical samples prior to confirming such findings in more clinically relevant populations. From an ethical perspective, this approach further ensures to not unnecessarily discomfort vulnerable participants. However, certain (small) effects may only become evident in clinical populations and thus may be overlooked in pre-clinical samples.

Overall, while there is no ideal study population in pre-clinical PTSD research, it is important to acknowledge and discuss the limitations of each study population chosen to ensure transparency.

6.8. Conclusion

The Renin Angiotensin System is primarily involved in blood pressure regulation. Yet, the central effects of ARB action have been increasingly unfolding, making them promising candidates for clinical applications in PTSD and anxiety.

In this DPhil thesis, I have investigated the role of ARBs in neurocognitive processing providing insights into memory formation and the human stress response – two key processes involved in PTSD psychopathology.

The main results show that ARBs act on brain structures at the intersection of visual processing and memory formation. Further, ARBs change the connectivity of structures within the memory system with structures involved in emotional processing and executive control.

It remains to be investigated how these results translate to peritraumatic processing preceding PTSD development – such as the dysfunctional integration of the traumatic event into the episodic memory system, including its associated visual cues.

In addition, I have shown that the proposed modulatory role of ARBs on the human stress response does not translate to a performance stress paradigm. Potentially, this is due to a lack of uncontrollability, unpredictability, and perceived threat – which are important characteristics for traumatic stressors. However, important interaction effects between ARB administration and hormonal contraception intake emerged suggesting that ARBs can restore a blunted cortisol stress response. While these results need to be replicated in targeted research, this thesis further highlights the need to investigate potential sex differences of central ARB action – especially since primarily male samples have been examined so far.

In addition, future research may move towards emotion-cognition effects. While an interdisciplinary approach is necessary to elucidate the underlying mechanisms of ARB action, it is equally important to adopt a pragmatic approach when moving forward to clinical translation.

Declaration of Authorship

I, Lorika Shkreli, declare that the content presented in this thesis is my original work, except the contributions from collaborative efforts detailed here. Chapter 2 and 3 have been adapted, extended, and formatted based on the published peer-reviewed journal article: Shkreli, et al (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. I am fully responsible for data management, data processing, data analysis, writing and the peer-review process. The conceptualisation, design and proofreading were conducted in collaboration with my primary supervisor Dr Andrea Reinecke, and the co-authors stated in the journal article. Due to the COVID-19 pandemic, including the departmental closure followed by strict health and safety regulations, recruitment of human participants was heavily disrupted requiring support with data acquisition as following:

(i) Data collection in chapter 2 and 3 was supported by DPhil student Theodora Thoroddsen.
(ii) A subset of the functional magnetic resonance imaging (fMRI) data presented in chapter 4 was acquired as part of a previously published study (Reinecke et al., 2018, Biol Psychiatry Cogn Neurosci Neuroimaging). Notably, this data was not included in the aforementioned publication and has not been analysed prior to this thesis.
(iii) Data collection and processing of saliva samples in chapter 5 was supported by MSc student Lauren Morse under my supervision.

Prior to statistical data analysis, processed saliva samples (chapter 5) were sent for assessment of cortisol levels to the laboratory of the Department of Biological Psychology, Technische Universtität Dresden, Germany (lead: Prof Clemens Kirschbaum). Training in fMRI analysis was provided by the Oxford Health Biomedical Research Centre and Wellcome Centre for Integrative Neuroimaging MRI Graduate Programme.

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