Manipulating the hypothalamic-pituitary-adrenal axis:

Effects on cognitive and emotional information processing and neural connectivity

---

A thesis submitted to the University of Oxford

for the degree of Doctor of Philosophy by

Kristin Schmidt

Green Templeton College, University of Oxford

Trinity term, 2016

Manipulating the hypothalamic-pituitary-adrenal axis: Effects on cognitive and emotional information processing and neural connectivity

Kristin Schmidt

Green Templeton College

Submitted for the degree of Doctor of Philosophy, Trinity Term 2016

Abstract

Despite extensive evidence documenting abnormal hypothalamic-pituitary-adrenal (HPA) axis functioning as a risk factor for the development of depression and other psychiatric disorders, and experimental evidence from acute stress manipulations, the effects of sustained cortisol alterations on clinically relevant cognitive-behavioural and neural processing remain poorly understood. The aim of this thesis was to characterise how non-acute changes in cortisol levels modify behavioural and neural biases implicated in stress-related disorders by following two complementary lines of evidence: firstly, by increasing cortisol via a direct pharmacological intervention; and secondly, by testing the ability of gut microbiota manipulations to alter cortisol reactivity.

The first study found that sustained increases in cortisol following 10-day administration of hydrocortisone were associated with altered memory and emotional processing in healthy volunteers. Specifically, participants receiving hydrocortisone showed enhanced recognition of emotional words, while their neutral memory performance was unaffected despite lower parahippocampal and occipital activation during viewing and encoding of neutral pictures. Furthermore, we found that resting-state functional connectivity between limbic-temporal regions of interest (amygdala and hippocampus) and the striatum (head of the caudate), as well as frontal and prelimbic cortices was decreased. In contrast, hippocampal and visual processing during negative facial expressions, and functional connectivity between the amygdala and the brainstem at rest, were increased in the hydrocortisone versus placebo groups. Overall, these findings suggest that non-acute increases in glucocorticoids enhance processing of emotionally salient information in limbic-temporal regions, which may modulate further neural mechanisms of sensory and homeostatic relevance. Enhancements in declarative emotional memory following hydrocortisone also implicate the modulation of amygdalar-hippocampal interactions by cortisol. Conversely, neutral stimulus processing was found to be either reduced or unaffected across a number of cognitive and memory domains. A specific increase for negative processing was further supported by poorer self-reported well-being at the mid-point of the study in participants receiving hydrocortisone.

In a separate study exploring the ability of prebiotic supplements to affect cortisol reactivity and emotional processing, a Bimuno-galactooligosaccharide prebiotic was found to reduce the waking cortisol response and increase positive versus negative attentional processing in healthy volunteers. While these effects were not found to be associated, they provide initial promising evidence of the ability to target the HPA axis and emotional processing via the gut microbiota in humans.

Overall, this thesis supports the idea that stress-induced physiological changes after prolonged or repeated cortisol exposure are associated with neural and behavioural alterations, which in turn have been crucial in understanding neuropsychological mechanisms underlying psychiatric disease. A better stratification of the effects of sustained HPA axis alterations on psychiatrically relevant cognitive-emotional domains and neural mechanisms thus remains of high priority.

DECLARATION

The studies presented in this thesis represent my own work, completed under the supervision of Prof. Catherine Harmer and Prof. Philip Cowen. Financial support for the studies was provided by a studentship from the Medical Research Council and the Department of Psychiatry at the University of Oxford.

The prebiotics study was supervised by Dr. Philip Burnet; recruitment and data collection for this study were supported by Mr. Steven Errington, and Mrs. Li Chen carried out the salivary cortisol analysis. The prebiotics study received further financial support by the BBRSC, Clasado Ltd., and a Wellcome Trust Vacation Scholarship to Steven Errington (SE). A paper based on the prebiotics study presented in Chapter 6 has been published in *Psychopharmacology*:

- Schmidt, K., Cowen, P. J., Harmer, C. J., Tzortzis, G., Errington, S., & Burnet, P. W. J. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology*, *232*(10), 1793–1801.

Mass spectrometry analysis of urinary free cortisol values as described in Chapter 2 was provided by Dr. Helen Fields (Leeds Teaching Hospital NHS Trust).

Word count: 42'600

ACKNOWLEDGEMENTS

There are a great number of people without whom this thesis would not have been possible, and who made the experience a rewarding one. My deepest thanks go to all of them.

First off, I would like to thank my supervisors, Prof. Catherine Harmer and Prof. Philip Cowen, who were instrumental in helping me develop towards independence as a researcher. Invaluable direction and knowledge were generously shared by many mentors and colleagues, most notably Prof. Caroline Pond, Dr. Abbie Pringle, Dr. Nicola Filippini, Dr. Nisha Singh, Dr. Corinna Klinge, and Dr. Hanneke den Ouden. All of their patient guidance helped to direct (often impossible) ideas into tangible outcomes, most notably during the analysis and writing stages.

The hydrocortisone study would have been unmanageable without help during the stages of data collection and analysis, and countless discussions and ideas regarding the interpretation of the data. Notably, Dr. Nicola Filippini, Dr. Sana Suri, Mr. Patrick Pflanz, Dr. Jacquie Scholl, and Dr. Matthew Warren (all MRI analysis), Dr. Mike Browning (medical screenings and MRI analysis), and Dr. Beata Godlewska (medical screenings), and Dr. Helen Field (mass spectrometry analysis) were exceedingly generous and kind in contributing their valuable expertise and time. Finally, special thanks go to Dr. Philip Burnet for having me on board for the prebiotics study, which was carried out with the support of Mrs. Li Chen and Mr. Steven Errington.

To each and every one of my friends, I am thankful for being a part of your life and sharing many wonderful experiences. You make difficult times bearable and great moments exceptional, and I couldn't ask for better companions. I hope to know you for many years to come (and make up for any lack of time, patience, and flexibility that I have shown recently).

Sometimes last, but never least — to my family, thank you. Your unconditional love, support, and humour never fail to provide strength and laughter. I wouldn't have made it here without you.

TABLE OF CONTENTS

ABBREVIATIONS

ACC	Anterior cingulate cortex
ACTH	Adrenocorticotropic hormone
ALE	Adverse life event
ANOVA	Analysis of variance
AVLT	Auditory Verbal Learning Task
BDI	Beck Depression Inventory
BFS	Befindlichkeits-scale
BOLD	Blood-oxygenation-level dependent
CAR	Cortisol awakening response
CEN	Central executive network
CFS	Continuous flash suppression
CRH/F	Corticotropin-releasing hormone / factor
CRHR1	Corticotropin-releasing hormone receptor 1
DMN	Default-mode network
EPI	Echo planar imaging
EPQ	Eysenck Personality Questionnaire
FEPT	Facial expression perception task
FERT	Facial expression recognition task
(f)MRI	(functional) magnetic resonance imaging
FOV	Field of view
GLM	General linear model
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
ICA	Independent Component Analysis
MDD	Major depressive disorder
MR	Mineralocorticoid receptor
MTL	Medial temporal lobe
NART	National adult reading test
PANAS	Positive and negative affect scales
PFC	Prefrontal cortex
PSRS	Perceived stress reactivity scale
PSS	Perceived stress scale
PTSD	Post-traumatic stress disorder
PVN	Paraventricular nucleus
ROI	Region-of-interest
rsFC	Resting-state functional connectivity
RSN	Resting-state network
SCA	Seed-based connectivity analysis
SD	Standard deviation
SEM	Standard error of the mean
SN	Salience network
SSRIs	Selective serotonin reuptake inhibitors
STAI	State-Trait Anxiety Inventory
TE	Echo time
TR	Repetition time
UFC	Urinary free cortisol
VAS	Visual analog scales
5-HTTLPR	Serotonin-transporter-linked polymorphic region

CHAPTER 1: GENERAL INTRODUCTION

1.1. Overview

Chronic or excessive stress is known to impair cognitive function and contribute to the development of debilitating psychiatric disorders such as depression and anxiety. Primary and secondary abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, which under healthy conditions functions as a highly adaptive system maintaining homeostasis in the face of internal and external stressors, play a central role in the these impairments (Cowen, 2009; Cranston, 2014; Finlay-Jones & Brown, 2009; Pariante & Lightman, 2008). An improved characterisation of the effects of the HPA axis and its end product, cortisol, on behavioural and neural functioning thus remains to be of high clinical and theoretical relevance, particularly within the framework of neuropsychological models relevant for understanding the course of and recovery from psychiatric disease. Through projects manipulating the HPA axis over a longer (non-acute) time span, this thesis sought to clarify the role of sustained alterations in cortisol levels in modulating cognitive and emotional processing and subjective well-being, focussing on biases that are evident in psychiatric symptomatology. The projects followed two complementary lines of investigation to delineate the cognitive-emotional mechanisms affected and their neural substrates: a pharmacological intervention study in healthy volunteers that directly increased glucocorticoid levels, and a novel approach attempting to target the HPA axis through manipulations of gut microbiota. This first chapter will selectively review research findings that implicate the HPA axis in psychiatric disorders, focussing on depressive and anxiety disorders. A brief overview of key cognitive and emotional processing abnormalities and associated models of disease and recovery follows. Reviewing how altered cortisol levels impact these biases highlights an evidence gap relating to the effects of sustained cortisol alterations in humans, which this thesis attempts to address.

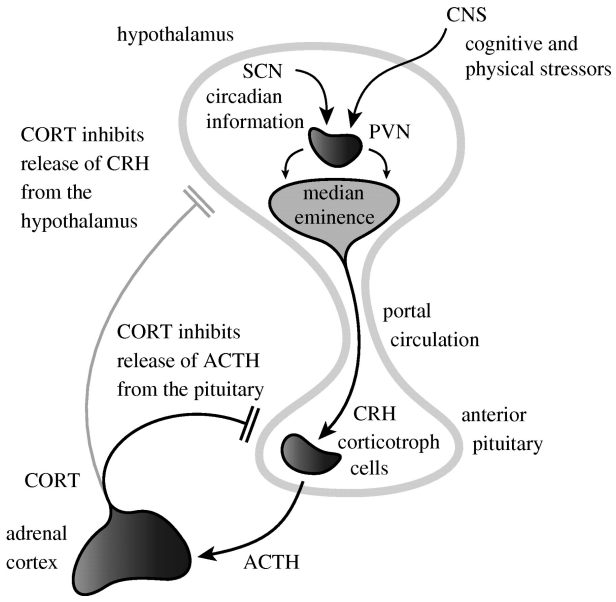
1.2. Psychiatric relevance of the HPA axis

1.2.1. Functions of the HPA axis

1.2.1.1. Homeostasis & acute stress

Under optimal pre- and postnatal development, the HPA axis is programmed to respond to changing demands and re-establish homeostasis (McEwen, 2007; McEwen & Wingfield, 2010), and to coordinate an organism's response to external and internal stress (Levine, 2005). These functions are coordinated via signals from central and peripheral networks, primarily mediated within a self-regulatory negative feedback loop via the release of its principal glucocorticoid hormone, cortisol (corticosterone in rodents) (Holsboer & Ising, 2008 see **Figure 1-1**). Importantly, the regulation of internal homeostatic and other downstream mechanisms within the HPA axis occurs via cyclical patterns of cortisol release (S. Chan & Debono, 2010). Cortisol's circadian rhythm has its peak during the main active period in the morning and decreases throughout the day and evening, reaching its lowest levels during the night (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Weitzman et al., 1971). In addition, rapid feedback mechanisms of the HPA axis lead to pulsatile patterns in the release of cortisol, with peaks and troughs occurring in the order of 10-20 minutes (Sarabdjitsingh, Conway-Campbell, et al., 2010; Walker, Terry, & Lightman, 2010).

Figure 1-1. The key components of the HPA axis & its negative feedback loop. Reprinted from Walker et al. (2010), with permission from The Royal Society © 2010.



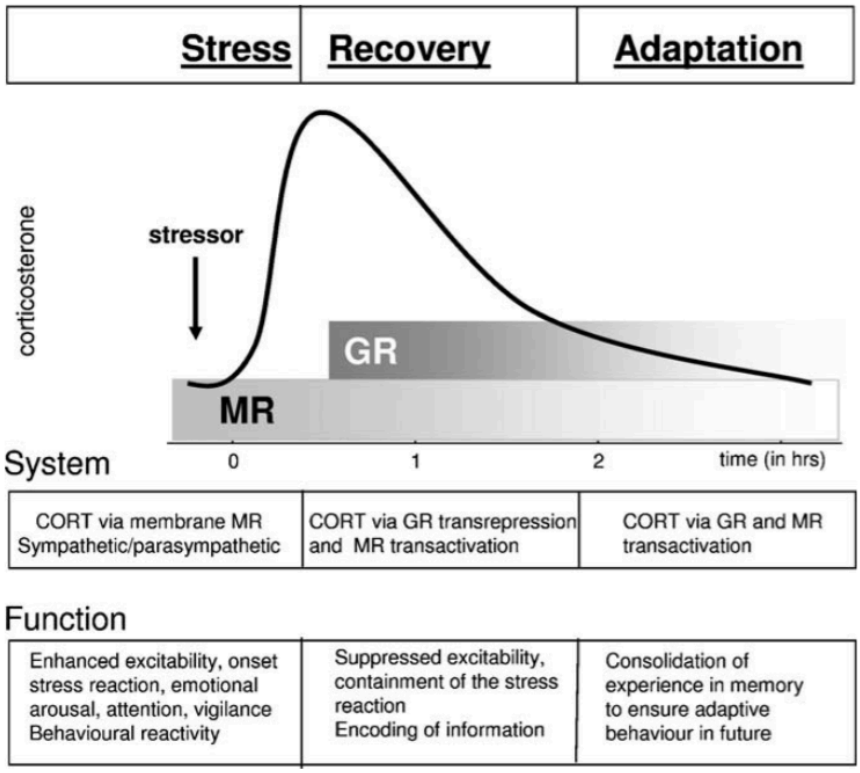
In addition to these regulatory patterns, external or internal stress activates the HPA axis and its co-ordination of the physiological response to stressors (see De Kloet, Joëls, & Holsboer, 2005; McEwen, 2007 for reviews). Specifically, somatic stimuli or psychological challenges can activate the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). The brain peptide CRH acts as a key regulatory mechanism of the HPA axis, stimulating synthesis and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary via increased pro-opiomelanocortin (POMC) transcription. Increases in ACTH in the bloodstream in turn stimulate increased cortisol release from the adrenal cortex, superimposed on circadian and ultradian fluctuations (Holsboer & Ising, 2008; Lightman, 2008). Finally, heightened cortisol concentrations in the bloodstream act to mobilise and store energy for appropriate downstream responses to stress and initiate an appropriate end to the stress response by acting on central targets including the hypothalamus in a negative feedback loop (De Kloet et al., 2005; Lightman, 2008).

1.2.1.2. Cortisol

As outlined, the response to acute stress is predominantly coordinated by the main end product of the HPA axis, cortisol (see **Figure 1-2**), a steroid hormone that reaches the majority of cells in the body. Cortisol crosses the blood-brain barrier where it exerts its effects via actions on widely distributed glucocorticoid receptor (GR) and mineralocorticoid receptor (MR; Pariante, 2004; Pascual-Le Tallec & Lombès, 2005; Sarrieau, O'Donnell, Alonso, & Meaney, 1996; Watzka, Beyenburg, et al., 2000; Watzka, Bidlingmaier, et al., 2000). Both are densely distributed across limbic regions such as the hippocampus, amygdala, and septum (McEwen, 2007), with GR also abundantly represented in the PVN and ascending aminergic neurons, and a high distribution of MR within the PFC (Herman et al., 2003). The MR overall has an approximately tenfold higher affinity for cortisol compared to the GR, which leads to the latter being primarily activated when glucocorticoid levels are high, such as under conditions of stress (De Kloet et al., 2000; De Kloet, Karst, & Joëls, 2008; Groeneweg, Karst, De Kloet, & Joëls, 2012; Joëls, Karst, Derijk, & De Kloet, 2008). Both GR and MR mediate glucocorticoid actions on complex downstream processes via

genomic and non-genomic actions in a time- and dose-dependent manner (De Kloet et al., 2008; Pariante, 2006). In the cell nucleus, GR and MR act as nuclear receptors involved in gene transcription (Evans & Arriza, 1989; Reul & De Kloet, 1985), whereas the same receptor proteins exert rapid non-genomic actions at the cell membrane (Joëls et al., 2008; Karst et al., 2005; Karst, Berger, Erdmann, Schutz, & Joels, 2010). Recent evidence indicates that the membrane-accessible receptors have a relatively low affinity for cortisol compared to the nuclear receptors, and may thus be particularly important in the regulation of stress-related events (Karst et al., 2005).

Figure 1-2. Phases of the stress reaction and recovery from stress in relation to glucocorticoid release. Reprinted from Oitzl et al. (2010), with permission from Elsevier © 2010.



A crucial function of cortisol in the brain is to initiate the self-regulatory negative feedback mechanisms of the HPA axis (McEwen & Gianaros, 2011; Sapolsky, Meaney, & McEwen, 1985). In addition to the pituitary and hypothalamus, the main glucocorticoid target regions of the medial temporal lobe (MTL; via the hypothalamus), amygdala and prefrontal cortex (PFC) are increasingly recognised as having important regulatory functions within the HPA axis (De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998; Dedovic et al., 2009; Herman, Ostrander, Mueller, &

Figueiredo, 2005). A hippocampal response, in particular, forms a necessary component in eliciting a cortisol response to stress (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004; Buchanan, Tranel, & Kirschbaum, 2009), and hippocampal (e.g. Abercrombie et al., 2011; de Quervain et al., 2003) and amygdalar (e.g. Henckens, van Wingen, Joels, & Fernandez, 2010; Lovallo, Robinson, Glahn, & Fox, 2010) regions are also the loci most reliably associated with functional activation following glucocorticoid administration.

1.2.1.3. Wider impact of HPA axis & cortisol

In addition to direct glucocorticoid mechanisms appropriately sustaining and terminating the stress response, acute stress involves the coordination of widespread physiological mechanisms, most markedly the regulation of the sympathetic nervous system via rapid increases in catecholamines (noradrenaline) from the locus coeruleus (Chrousos, 2009). Jointly, these alterations lead to widespread metabolic, hormonal, and neurotransmitter responses such as neuromodulatory effects via monoaminergic neurotransmitters and glutamate, and the modulation of glucose metabolism, immunological, and inflammatory processes (Joëls & Baram, 2009; Rohleder, 2012). Changes in the HPA axis thus exert a global influence on brain and behavioural function, including shifts in attention and cognition, mediated in in part by their diffuse actions on cortical and subcortical regions. Conversely, HPA axis functioning is modulated by wide-ranging physiological changes, with reliable activation in response to e.g. inflammation (Straub, Buttgereit, & Cutolo, 2010) and hunger (Ott et al., 2011), while psychological stressors have been found to elicit more varied and inconsistent responses (Burke, Davis, Otte, & Mohr, 2005).

1.2.1.4. Adaptive vs. maladaptive functioning

When functioning efficiently, these effects constitute an adaptive allostatic response associated with functional and physiological enhancements, in particular to coordinate appropriate actions to the encountered stressors (De Kloet et al., 2005, 1998). However, in contrast to the acute response to stress, sustained or excessive exposure to stressors (particularly when encountered early in life) and genetic risk factors can lead to chronic dysregulations in HPA axis mechanisms, including blunted feedback sensitivity, slow responsivity, or altered rhythmicity, associated with disruptions

to the timely conclusion of the stress response and recovery of homeostasis (Bogdan, Pagliaccio, Baranger, & Hariri, 2016; Bowers & Yehuda, 2016; Conrad, 2008; Frodl & O'Keane, 2013; Gądek-Michalska, Spyrka, Rachwalska, Tadeusz, & Bugajski, 2013; Herman, 2013; Radley et al., 2011). Regardless of the initial factors of excessive strain, such as encountering extreme stress or repeated moderate stressors, the HPA axis' self-regulatory mechanisms can then become detrimental, bringing about pathophysiological effects on a range of physiological, including neural, systems, and exacerbating abnormal rhythmicity and absolute levels of cortisol (Marin et al., 2011; McEwen, 1998). Abnormalities in cortisol levels and HPA axis regulation have been found across a range of psychiatric phenotypes (see D. Baumeister, Lightman, & Pariante, 2014 for a recent review). However, attempts to understand the association between cortisol levels and symptoms, maintenance, relapse, and recovery in a straightforward manner have failed to yield satisfactory results (Joëls, 2011).

1.2.2. HPA axis in psychiatric disease

1.2.2.1. Genes x Environment and development in early life

The development of the HPA axis is impacted by genetic, prenatal, and childhood environments, including internal developments such as a healthy gut microbiota and immune system (Bellavance & Rivest, 2014; Dinan & Cryan, 2012; Frodl & O'Keane, 2013; Leonard, 2005; Maniam, Antoniadis, & Morris, 2014; Pagliaccio et al., 2015; Schatzberg et al., 2014; Wasserman, Wasserman, & Sokolowski, 2010), as well as excessive stressors during the lifespan (Lupien, McEwen, Gunnar, & Heim, 2009) and normal ageing (Belvederi Murri et al., 2014). Any disruptions in these mechanisms can trigger altered functioning of the HPA axis, and the most promising findings emerge when factors such as genetic risk and family history, stressful life events (especially in early childhood), and disease severity are taken into consideration (Caspi, 2003; Charney & Manji, 2004; Engel, 1979; Gotlib, Joormann, Minor, & Hallmayer, 2008; Martin, Ressler, Binder, & Nemeroff, 2009; Schatzberg, 2015). According to such biopsychosocial models of psychiatric disease (Engel, 1979), a dysregulation in the HPA axis is linked to the vulnerability to, development, and maintenance of psychiatric mood and anxiety disorders. HPA axis

abnormalities appear to predispose individuals to higher vulnerability to "stress-related" disorders, can trigger the onset of an episode, and are associated with increased persistence of symptoms, suggesting that the complex interaction between genetic vulnerability and detrimental environmental factors converges on genetic risk factors increasing the sensitivity to stressful life events across development (Caspi, 2003; Kendler et al., 1995; Kendler & Gardner, 2011).

Genetic risk factors for psychiatric disorders have been extensively studied (Allen MG, 1976; Arguello & Gogos, 2012; Kendler et al., 1995; Smoller, 2016; Sullivan, Neale, & Kendler, 2000), although overall our understanding of genetic factors modulating the HPA axis and its involvement in psychiatric risk is still in its infancy (De Kloet & Derijk, 2004). Variations in the corticotropin-releasing hormone receptor 1 (CRHR1) protein, involved in the regulation of the HPA axis, are known to modulate the response to excessive stress (Wasserman et al., 2010), specifically having been shown to mediate the effects of childhood maltreatment on cortisol responsivity (Heim et al., 2009; Tyrka et al., 2009). Furthermore, studies suggest the short allele of the serotonin-transporter-linked polymorphic region (5-HTTLPR) is involved in mediating the association between cortisol reactivity and the risk to develop depression, potentially via altered neural responsivity (Caspi, 2003; Fisher et al., 2012; Goodyer, Bacon, Ban, Croudace, & Herbert, 2009; Gotlib et al., 2008; Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012; S. E. Murphy et al., 2012; Risch et al., 2009; Schipper et al., 2015; Wankerl et al., 2010). Carriers of the short allele have shown increased cortisol reactivity in response to stress tests (Gotlib et al., 2008), especially in short allele carriers with a history of stressful life events (Alexander et al., 2009). Rodent studies, which have found impaired behavioural and altered neurochemical profiles in heterozygous 5-HTT KO mice subjected to chronic levels of stress (e.g. Bartolomucci et al., 2010), support these findings. Additionally, FK506-binding protein 5 (FKBP5) has been associated with increased vulnerability to psychiatric disorders, particularly due to its ability to modulate stress sensitivity via altering GR signalling (Guidotti et al., 2013; Wagner et al., 2012; Xing et al., 2015). Furthermore, allelic variation for GR genes has been found to contribute significantly to cortisol dysregulation and increased risk of disease (see Schatzberg et al., 2014).

Crucially, the development of the HPA axis is further shaped by prenatal (Cottrell, Seckl, Cottrell, & Seckl, 2009) and differential exposure to stressors particularly early in life has the potential to trigger trajectories of resilience vs. risk (Heim et al., 2009; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Heim & Nemeroff, 2001). Exposure to prenatal stress and childhood maltreatment are associated with increased occurrence of psychiatric disease in adulthood (Anacker, O'Donnell, & Meaney, 2014; Bick & Nelson, 2016; Fonzo et al., 2015; Maniam et al., 2014; McGowan, 2013; Starr, Hammen, Conway, Raposa, & Brennan, 2014), thought to be mediated by detrimental molecular changes in the regulation of HPA axis responses (Anacker et al., 2014). Evidence for early-life influences on stress responsivity and vulnerability later in life, from both human (Alexander et al., 2009; Bick & Nelson, 2016; Goodyer et al., 2009; Gotlib et al., 2008; Kendler et al., 1995; Oitzl, Champagne, van der Veen, & De Kloet, 2010) and rodent (e.g. Zhang, Labonté, Wen, Turecki, & Meaney, 2012) studies implicate abnormal responsivity of the HPA axis as a marker of vulnerability to depression and anxiety.

1.2.2.2. Psychiatric disease status

While early-life programming of the HPA axis has the ability to confer a vulnerability to stressors later in life via genetic and environmental factors, abnormal functioning of the HPA axis in adolescence and adulthood, particularly in response to stressful or adverse life events (ALEs), may furthermore precipitate and facilitate disease onset (Lethbridge & Allen, 2008; Melchior et al., 2007). Overall, while cortisol reactivity has been linked with the likelihood of development or recurrence of depressive disorders in individual studies (Adam et al., 2010; Morris, Rao, & Garber, 2012; Vrshek-Schallhorn et al., 2013), a number of large cohort studies have found no or only weak associations between absolute increases in cortisol levels and depressive symptomatology (see Burke et al., 2005; Carnegie et al., 2014; Dietrich et al., 2013). Instead, it has been suggested that increased cortisol levels may be more usefully understood as an indicator of "general distress" in development and – when combined with other risk factors – as an emergence marker in sub-populations (Grynderup et al., 2013; Lewis, Jones, & Goodyer, 2016; Vedhara et al., 2003).

A number of studies have found that patients with depression show an augmented cortisol awakening response (CAR; Bhagwagar, Hafizi, & Cowen, 2005; Dienes, Hazel, & Hammen, 2013; Vreeburg et al., 2009), a rapid increase in cortisol levels upon waking in the morning that is thought to be a reliable indicator of acute HPA axis reactivity and at least partially regulated by the hippocampus (Fries, Dettenborn, & Kirschbaum, 2009; Pruessner et al., 1997). Increases in the CAR have been hypothesised to be particularly prominent in depression of the melancholic subtype (Lamers et al., 2013), and may be due to altered GR functioning, reflecting a reduced ability of the HPA axis to down-regulate its own activity (D. Baumeister et al., 2014). Findings of increased CARs have sometimes (Vreeburg et al., 2009), though not consistently (Masurier, Cowen, & Harmer, 2006; Strickland, 2002), been extended to individuals recovered from depression and at-risk adults (Dienes et al., 2013; van Santen et al., 2011). They have even been shown to predict time to recurrence of depression (Hardeveld et al., 2014), although reductions in the CAR have also been found to constitute a vulnerability factor for depression (Dedovic et al., 2010). Additional evidence for altered CAR as a vulnerability factor comes from studies in adolescents and young people, where increases in the CAR have been found in those with a parental history of depression (Douglas & Harmer, 2011; Mannie, Barnes, Bristow, Harmer, & Cowen, 2008; Mannie, Harmer, & Cowen, 2007), and linked with a higher risk of developing depression (Adam et al., 2010; Goodyer, Tamplin, Herbert, & Altham, 2000; Vrshek-Schallhorn et al., 2013).

In addition to findings of altered CARs, reports indicate that a subset of patients with major depressive disorder may exhibit hypercortisolaemia (see Herbert, 2012; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). Increases in HPA axis activity in depression, with associated increases in cortisol levels and hyperactivity of the pituitary and adrenal glands (Nemeroff & Vale, 2005) is thought to be at least partially due to reduced feedback inhibition (Pariante, 2006). In line with this, a number of reports document altered GR function and expression (Pariante, 2006; Pariante & Lightman, 2008; Pariante & Miller, 2001). Some, though not all, studies have found that abnormally increased HPA axis activity and subjective responses are evident following stress in patients with depression (Carpenter et al., 2009; Pariante &

Lightman, 2008). Finally, evidence for altered HPA axis sensitivity in depression also comes from findings of non-suppression of cortisol following administration of dexamethasone in patients, although this may be restricted to particular subtypes (Hori et al., 2014; Mokhtari, Arfken, & Boutros, 2013). While associations between absolute cortisol levels and depressive symptomatology may thus be limited (D. Baumeister et al., 2014), and absolute cortisol abnormalities show only marginal predictive or demarcating clinical usefulness, some measures of HPA axis activity appear to be sensitive indicators of risk or acute disease status of depression (Burke et al., 2005; Knorr, Vinberg, Kessing, & Wetterslev, 2010).

Increasingly, the importance of alterations in circadian and ultradian cortisol rhythms is recognised for understanding the symptoms of depressive and other psychiatric symptoms (Jagannath, Peirson, & Foster, 2013; Keller et al., 2006; S.-X. Li et al., 2013; Sarabdjitsingh, Spiga, et al., 2010). As a particularly useful marker, a smaller difference between morning and afternoon cortisol levels has been associated with increases in subjective reports of stress and sub-clinical anxiety (Vedhara et al., 2003), cognitive impairment (Johar et al., 2015; Schatzberg, 2015) and a higher odds ratios of future emergence of depression (Grynderup et al., 2013). Furthermore, increased afternoon cortisol levels (during quiescent hours) have been found in individuals with depression (Stetler & Miller, 2005; Strickland, 2002), which may involve altered GR (Schatzberg, 2015) and MR (Keller et al., 2006) function.

Importantly, these altered circadian release patterns appear to be particularly pronounced in depression with psychotic features, which has been theorised to constitute either a syndrome distinct from depression without psychosis, or at the severe end of a unitary depressive syndrome (Belanoff, Kalehzan, Sund, Ficek, & Schatzberg, 2014; Keller et al., 2006; Lewis et al., 2016; Schatzberg, 2015). Such stratification by depressive subtypes has been fruitful in yielding more reliable glucocorticoid disease markers (H. Baumeister & Parker, 2012). Overall, evidence suggests that findings between increased cortisol levels with psychotic depression are more consistent than for other subtypes, while increased cortisol levels are less pronounced found for endogenous and melancholic subtypes (reviewed in Stetler & Miller, 2011). Atypical depression, on the other hand,

has been associated with lower cortisol levels but elevated inflammatory and metabolic markers (Lamers et al., 2013). Thus, a number of inconsistencies evident in the findings of HPA axis activity in psychiatric disorders may emerge in part from limited diagnostic specificity, with HPA axis activity better mapping onto subtypes and dimensional aspects of symptoms rather than formal psychiatric diagnoses (Wolkowitz, Burke, Epel, & Reus, 2009).

In line with this, elevated HPA activity levels and reduced suppression of cortisol following dexamethasone appear to be closely associated with symptoms of psychosis (Belanoff et al., 2014; Mondelli et al., 2015; Pariante, 2004, 2009; Schatzberg et al., 2014), and have been shown to normalise following antipsychotic treatments (Belvederi et al., 2016). Furthermore, individuals at high risk of psychosis who went on to develop symptoms show increased volumes of the pituitary gland (Nordholm et al., 2013), supporting a potential causative role of abnormal HPA axis activity in the development of psychosis. However, patients with schizophrenia – frequently associated with symptoms of psychosis – have shown differential patterns in HPA axis activity to patients with depression, with reduced cortisol released in response to stress, specifically social stress (Ciufolini, Dazzan, Kempton, Pariante, & Mondelli, 2014). Schizophrenia has also been linked with a lower CAR, which in turn was associated with worse cognitive functioning and more severe positive symptoms (Aas et al., 2011; Mondelli, Dazzan, et al., 2010; Mondelli, Pariante, et al., 2010).

Disruptions in HPA axis responsivity have also been linked with functional changes in bipolar disorder, particularly symptoms of mania (Belvederi et al., 2016; A. H. Young, 2014). While the evidence base overall is much smaller than that for unipolar depression, bipolar disorder has been associated with increases in baseline cortisol and CAR, as well as blunted cortisol responses to the DEX challenge (see Belvederi et al., 2016). Elevations in cortisol and ACTH have been shown to precede and accompany manic episodes in bipolar disorder (D. Baumeister et al., 2014), and a recent meta-analysis suggests altered cortisol levels and responsivity extend to unaffected relatives of patients with bipolar disorder (Belvederi et al., 2016).

Finally, anxiety disorders are often comorbid with depressive disorders (Kret & Ploeger, 2015;

Sartorius, Bedirhan, Lecrubier, & Wittchen, 1996) and the two are closely linked in their emergence models of altered HPA axis responsivity to stressful life events and chronic stressors (Maniam et al., 2014). To some degree, subjective and physiological activation is a functional component of the stress response, and altered HPA axis activity in depression has been associated with symptoms of agitation (Min et al., 2012). However, the link between heterogeneous anxiety disorders and cortisol levels has not been fully elucidated. Overall, it appears that the CAR is sometimes increased, although only reliably so for subtypes of anxiety such as panic disorder or anxiety comorbid with depression, while cortisol levels measured following dexamethasone suppression or in the afternoon have shown no reliable deviations from those in healthy controls (Faravelli et al., 2012). However, promising evidence is emerging from avenues of research that link anxiety and HPA axis activity in a number of disorders such as irritable bowel syndrome and burn-out, which are often comorbid with anxious symptomatology. In these disorders, interactions of stress responsivity with other systems such as the gut microbiota and immune system appear to play a key role (Crumeyrolle-Arias et al., 2014; Dinan & Cryan, 2012).

Within anxiety disorders, post-traumatic stress disorder (PTSD) forms a special case in its relation to HPA axis dysfunction, in that it is strongly associated with excessive stress experienced under traumatic conditions (Cranston, 2014). Specifically, the HPA axis response immediately following a traumatic event has been shown to predict onset of PTSD, with lower cortisol responses following the trauma and higher cortisol suppression to dexamethasone within 24 hours (Morris & Rao, 2013), as well as lower morning and higher afternoon cortisol levels within one week of trauma exposure linked with higher risk of PTSD development (Aardal-Eriksson, Eriksson, & Thorell, 2001). Nevertheless, inconsistent findings of cortisol activity in PTSD have reported both increased levels and null effects (Schalinski, Elbert, Steudte-Schmiedgen, & Kirschbaum, 2015; Steudte et al., 2013), findings that may be mediated by the type of trauma experienced. A recent meta-analysis found no differences in cortisol levels of PTSD patients overall, although reductions were reported in individual studies, and exposure to trauma was associated with increased cortisol suppression to dexamethasone challenge (Berridge, 2009; Cranston, 2014; McGowan, 2013; Shvil, Rusch, Sullivan,

& Neria, 2013).

1.2.2.3. Treatment response, predictors, & relapse

HPA axis markers have also been investigated in relation to treatments of and recovery from psychiatric illness. Beneficial effects on the HPA axis have been found with non-glucocorticoid antidepressants such as selective serotonin reuptake inhibitors (SSRIs; Pittenger & Duman, 2008), with lower cortisol levels reported in patients receiving antidepressant medication compared to those not on antidepressants (Barnhofer, Kuehn, & de Jong-Meyer, 2005). Long-term treatment with the widely prescribed SSRI, citalopram, has been shown to reduce HPA axis responsiveness, and the degree of symptom improvement was predicted by this decrease in cortisol responsivity (Nikisch et al., 2005).

Compounds directly targeting glucocorticoids have been tested for their potential to act on the HPA axis as antidepressants, with mixed findings (Holsboer, 2001; Holsboer & Ising, 2008; Thomson & Craighead, 2007; A. H. Young, 2006). These treatments, largely consisting of GR antagonists, cortisol synthesis inhibitors, and CRF antagonists, have yielded some positive results (A. H. Young, 2006), which suggest that an improved understanding and targeting of receptor specificity and improved modulation of HPA axis rhythmicity may yield promising developments in the pharmacological management of abnormal HPA functioning (Anacker & Pariante, 2012; Anacker, Zunszain, Carvalho, & Pariante, 2011; Pariante & Miller, 2001; Sarabdjitsingh, Spiga, et al., 2010). Another line of research argues for their use as augmentation therapy, investigating their potential to enhance the neurochemical response to other forms of antidepressants (D. A. Johnson, Grant, Ingram, & Gartside, 2007). Overall, however, clinical studies have found for existing compounds to show limited treatment efficacy so far, with the exception of some GR antagonists in psychotic depression (Schatzberg, 2015).

Based on findings that elevated levels of glucocorticoids during depression were normalised after successful treatment with either pharmacological antidepressants (Heuser et al., 1998; Vythilingam et al., 2004) or electroconvulsive therapy (Nemeroff, Bissette, Akil, & Fink, 1991), it has, however,

been suggested that in those patients who exhibit it when depressed, normalisation of hypercortisolaemia is essential for recovery (Holsboer & Ising, 2008). Increased levels of cortisol in response to pharmacological challenge at the start of treatment (Zobel, Yassouridis, Frieboes, & Holsboer, 1999), at discharge (Zobel et al., 2001), and in remission (Morris et al., 2012; Zobel et al., 1999) have been associated with increased rates of relapse in depression. Furthermore, increased cortisol responses to dexamethasone have also been shown to predict poorer symptom remission in response to therapy in PTSD (Nijdam, van Amsterdam, Gersons, & Olff, 2015). Regardless of the disparities in findings of HPA axis abnormalities as markers of development and symptomatology in psychiatric illnesses, HPA axis normalisation thus appears to form an important component of successful recovery.

1.2.3. Psychiatric findings in glucocorticoid abnormalities

1.2.3.1. Hormonal disorders

Cortisol abnormalities also emerge from hormonal disorders, most prominently Addison's disease (primary adrenal insufficiency characterised by a lack of endogenous cortisol and aldosterone production; Schultebraucks, Wingenfeld, Heimes, Quinkler, & Otte, 2015) and Cushing's syndrome (characterised by excessive endogenous exposure to cortisol e.g. due to pituitary or adrenal tumours; Andela et al., 2015). In patients receiving cortisol replacement therapy for Addison's disease, poor subjective well-being is reported, with recent methodological advances highlighting the potential for restored ultradian rhythmicity to alleviate these symptoms (Kalafatakis et al., 2016; Sarabdjitsingh, Spiga, et al., 2010). Patients with Cushing's syndrome report a poor quality of life overall, with a high incidence of psychiatric symptoms, especially depression, which largely remit when cortisol normalises (Pivonello et al., 2015; Sonino & Fava, 1998; Sonino, Fava, Raffi, Boscaro, & Fallo, 1998; Sonino, Nicoletta, Fava, Giovanni A., Belluardo, Girelli, & Boscaro, 1993; Starkman, 2013; Starkman & Schteingart, 1981; Starkman, Schteingart, & Schork, 1986). While associated mood abnormalities appear to be directly linked to HPA axis status (rather than secondary to disease diagnosis), the mechanisms by which glucocorticoids are implicated in the exact symptomatology remain to be characterised.

1.2.3.2. Steroid medications

Given their widespread systemic effects, exogenous glucocorticoids are also widely used as medical treatments. Reports linking their administration with altered mood and psychiatric symptoms in a subset of patients emerged shortly after they first came into use and are well-established (Naber, Sand, & Heigl, 1996). In particular, corticosteroid therapy is associated with a higher incidence of developing a psychiatric illness, sleep disturbances, altered energy levels, and subclinical symptoms of psychosis, (hypo)mania, anxiety, and depression (Fardet, Petersen, & Nazareth, 2014; Judd et al., 2014). The likelihood of experiencing these symptoms increases with higher doses and repeated courses of treatment (J. R. Curtis et al., 2006; Fardet et al., 2014), with overall estimates of prevalence ranging from 3% for the development of a clinically significant manic episode to 12% to 25% for symptoms of hyperactivity and irritability, respectively (Judd et al., 2014). Reports of symptoms differ depending on the time course of administration, with manic symptoms often apparent within days of first starting treatment (Brown, Suppes, Khan, & Carmody, 2002; Naber et al., 1996; Wada et al., 2001), and depression more closely associated with longer-term administration even at low doses (Bolanos et al., 2004; Fardet et al., 2014; Frol et al., 2013; Gift, Wood, & Cahill, 1989), with some evidence of depression persisting after the discontinuation of chronic treatment (Fardet, Nazareth, Whitaker, & Petersen, 2013). While the majority of patients do not experience symptoms of clinical severity, reports of less severe but persistent alterations in well-being and functioning especially at high doses and when administered chronically (J. R. Curtis et al., 2006; Judd et al., 2014) point to the profound impact of altered glucocorticoid signalling on the brain, particularly when administered chronically. Nevertheless, exactly how cortisol influences the development of psychiatric symptoms over time remains unclear (Wolkowitz et al., 2009).

Some inconsistencies in findings are likely due to the large variability in individual responses to HPA axis changes, which is furthermore heterogeneous across different demographics, gender, and moderated by trait differences (Abercrombie et al., 2011; Henckens, Klumpers, et al., 2015; Hruschka, Kohrt, & Worthman, 2005; Otte et al., 2005). Studies have suggested that stress-related

disorders are more prominent in females, with women more likely to suffer from PTSD or depression than males (Kendler et al., 1995; Kendler & Gardner, 2011). Altered susceptibility to glucocorticoid processes at the neural level may contribute to an increased susceptibility to stress in females (e.g. via CRF), and thus to this discrepancy in prevalence (Bangasser & Kawasumi, 2015).

1.3. Neuropsychological models

1.3.1. Diagnostics & emergence of models

Promising research regarding cortisol's impact on psychiatric symptoms has emerged from a drive towards increasingly subtle stratifications of clinical syndromes (H. Baumeister & Parker, 2012; Veen et al., 2011; Wardenaar et al., 2011). While clinical classifications have been useful in the therapeutic management of psychiatric disease, evidence increasingly points to the restricted validity of these criteria as discrete categories that can inform pathophysiology. From a clinical standpoint, the large amount of symptom variability and comorbidity point to the heterogeneity of and overlap between psychiatric diagnoses (Brodbeck et al., 2014; Corral-Frías et al., 2015; Kret & Ploeger, 2015; Lewis et al., 2016; Robbins, Gillan, Smith, de Wit, & Ersche, 2012; Sheline, 2000). Scientifically, inconsistent links with biological markers may in part be related to this poor diagnostic validity, which has been addressed with increasing use of a more dimensional, cross-diagnostic understanding of symptoms and their neurobiological basis (Kemp & Felmingham, 2008; Kober et al., 2008; Wardenaar et al., 2011). This is particularly relevant to understanding the role of cortisol-related impairments, which appear to be not directly causal to a specific disorder but may instead contribute to the emergence, maintenance, and remittance of disease course and symptomatology across a number of disorders (Veen et al., 2011; Wolkowitz et al., 2009).

Revisiting the role of cortisol abnormalities in psychiatric symptoms is particularly timely given methodological and theoretical developments in neuropsychiatry. Increasingly, cognitive, social, and biological theories of psychiatric disease have been bridged by methodological advances in cognitive neuroscience, allowing models to converge towards an integrated and refined understanding of the aetiology, symptomatology, and recovery of illnesses via neural and

behavioural mechanisms (Kemp & Felmingham, 2008; Kober et al., 2008; Kret & Ploeger, 2015). Of particular importance (especially within mood and anxiety disorders) has been the development of a large evidence base for altered neural and behavioural responses that can be closely linked to the development and maintenance of symptoms (Harmer, 2010; Peckham, McHugh, & Otto, 2010; Roiser, Elliott, & Sahakian, 2011). This follows on from early cognitive theories, which posit that negative biases in the cognitive processing and memory of self-referential information were key to pathological schemata and to social and behavioural impairments in patients with depression (see Beck, 2008).

1.3.2. Findings in patients and healthy volunteers

Tasks ranging from reward-related processing to emotional memory show that biases in the processing of affective or emotional information are a consistent feature of depression, and to some extent, in those vulnerable to developing depression (Elliott, Zahn, Deakin, & Anderson, 2011; Eshel & Roiser, 2010; Roiser et al., 2011). In accordance with findings that these biases normalise with recovery (Roiser et al., 2011; Sheline et al., 2001) and may predict symptom improvement (Siegle, Carter, & Thase, 2006), a central line of research has focused on refining the use of these emotional biases to predict treatment efficacy and to understand the neuropsychological mechanisms of pharmacological treatments. Data indicates that commonly prescribed antidepressants consistently change these processing abnormalities in the direction of decreased negative biases (Harmer, Goodwin, & Cowen, 2009), which is in line with cognitive theories of depression (Beck, 2008). These findings are now central to a line of research focussed on refining these emotional biases as predictors of clinical treatment efficacy, and may allow an estimation of the usefulness of (psychological or pharmacological) treatments by providing a "necessary final pathway […] of clinical efficacy" (Harmer, Cowen, & Goodwin, 2011). While models are not limited to emotional processing, these form some of the most comprehensive evidence available, especially for the "stress-related" disorders of depression and anxiety.

1.3.3. Cortisol in neuropsychological models

While the impact of some neurotransmitters, particularly serotonin and dopamine, on emotional processing and cognition is starting to be delineated (Clark, Chamberlain, & Sahakian, 2009; Cowen, 2008; Dayan & Huys, 2008; Harmer, 2008), non-acute changes in neurohormones such as cortisol have not been fully characterised with regards to functional changes that may be important for understanding symptoms (Cowen, 2009). The neural-behavioural mechanisms that appear to be altered by cortisol manipulations are strikingly similar to – and in some cases, have been shown to underlie – neural and functional differences in psychiatric populations compared to healthy controls (Erickson, Drevets, & Schulkin, 2003). However, despite the abundance of research implicating a dysfunctional HPA axis in depressive and anxiety disorders (e.g. Holsboer, 2000; Pariante & Miller, 2001) and detailed evidence of impairments such as abnormal corticosteroid receptor signalling and neuroplastic changes (Holsboer, 2000; Krishnan & Nestler, 2008; Pariante & Miller, 2001), the exact effects of glucocorticoid changes on cognitive and emotional biases in depression are still not fully understood. Specifically, the most extensive evidence documents the effects of acute changes in cortisol (see Putman & Roelofs, 2011 for a review), highlighting a scarcity of studies on sustained cortisol alterations that may bridge our understanding of the molecular mechanisms, immediate functional effects, and clinical findings.

1.4. Neural and behavioural effects of cortisol

1.4.1. Structural & physiological changes

1.4.1.1. Glucocorticoid effects

In contrast to the largely indirect links between HPA axis changes and psychiatric symptomatology, cortisol's direct effects on the physiology of the brain are well-documented. The ability of abnormal cortisol secretion to produce widespread alterations of neural structures and function is thought to be instrumental in the development and maintenance of psychopathologies. While short-term, controllable stress can increase neurogenesis and learning in response to changing demands of the environment (McEwen, 2007), a return in hormone concentrations to pre-

stress levels leads to an adaptive response, with gene-mediated corticosteroid actions reversing enhanced excitability (Joëls, Karst, Krugers, & Lucassen, 2007). On the other hand, sustained hypercortisolaemia is associated with region-specific neurotoxic effects and structural changes, which may be directly responsible for at least a subset of the functional impairments of chronic stress (De Kloet et al., 2005). These processes are primarily mediated via GR and MR receptors, with subsequent extensive alterations in the excitability and activation of neurons leading to reduced grey matter volume in regions including the hippocampus and medial temporal lobe, amygdala, hypothalamus, and prefrontal cortex (Brown, Woolston, & Frol, 2008; De Kloet et al., 1998; Karst et al., 2002; MacQueen & Frodl, 2011; Mitra & Sapolsky, 2008; Sapolsky, 2000).

The effects of glucocorticoids have been most comprehensively studied in the hippocampus, where they stimulate excitatory neurotransmitters (e.g. glutamate) and eliminate activity-dependent increases in growth factors (lowering dendritic branching in response to stimuli), leading to initially reversible remodelling (Campbell & Macqueen, 2004). With prolonged and excessive elevations in cortisol, neurotoxic effects extend to altered dendrite and spine morphology and suppression of adult neurogenesis (Joëls et al., 2007), affecting hippocampal structure and function via hormones, peptides, and transmitters (Brown, Rush, & McEwen, 1999; Conrad, 2008; Joëls & Baram, 2009). Within the medial temporal lobe, specific regions of the hippocampal complex, and particularly in the hippocampal head appear to be more susceptible to atrophy and stress effects (Duman & Monteggia, 2006; Frodl & O'Keane, 2013; Sapolsky, 2000).

1.4.1.2. Potential mechanisms

While these structural alterations are of high functional and clinical relevance, the majority of findings have emerged from rodent studies, necessitating increased translation of physiological mechanisms of hypercortisolaemia in humans (Anacker & Pariante, 2012; Pariante & Lightman, 2008). Nevertheless, the scarce direct evidence from human studies is in line with pronounced rapid and long-lasting effects of increased cortisol on hippocampal physiology. Early MRI reports confirmed reduced hippocampal volume in a subset of patients with Cushing's syndrome (chronic hypercortisolaemia), with larger reductions associated with higher cortisol levels (Starkman,

Gebarski, Berent, & Schteingart, 1992). Imaging studies in healthy volunteers have found cortisol to rapidly reduce glucose metabolism (De Leon et al., 1997) and increase BOLD activation at rest 10-20mins post-infusion of hydrocortisone, plausibly via non-genomic GR/MR signalling (Symonds, McKie, Elliott, William Deakin, & Anderson, 2012). Intriguingly, a recent within-subjects crossover study showed that a 3-day course of (160mg/day) hydrocortisone was associated with rapid reductions in hippocampal volume compared with placebo, which were related to concomitant increases in cortisol levels (Brown et al., 2015). This provides the first evidence of structural alterations after brief glucocorticoid exposure in humans, compared to previous null results (Scheel, Ströhle, & Bruhn, 2010; Tessner, Walker, Hochman, & Hamann, 2006). Convincing evidence also comes from patients receiving chronic glucocorticoids as medical treatments, who have been shown to have smaller hippocampal volumes and altered N-acetyl aspartate ratios compared with control subjects (Brown et al., 2004). Importantly, structural damage is thought to lead to exacerbate dysregulated HPA axis processes due to reduced hippocampal feedback inhibition (by cortisol) on CRH secretion, thereby resulting in inefficient termination of high hormone concentrations and further hippocampal damage (Sapolsky et al., 1985). Additional exposure to stressors, albeit at brief durations, may then be met with altered functional responses, "including a sensitised activation phase and associated inadequate normalisation of brain activity" (Joëls et al., 2007; Sapolsky, 2000).

1.4.1.3. Clinical evidence

The clinical relevance of neurotoxic effects as outlined by this "glucocorticoid cascade hypothesis" (Frodl & O'Keane, 2013; Sapolsky, 1996) is supported by evidence of reduced hippocampal volumes in patients with chronic or severe psychiatric disease, especially PTSD (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005) and depression (for reviews and meta-analyses, see Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012; Campbell & Macqueen, 2004; Cole, Costafreda, McGuffin, & Fu, 2011; Frodl & O'Keane, 2013; Lorenzetti, Allen, Fornito, & Yücel, 2009; Schmaal, Veltman, et al., 2015; Sheline, 2000; Videbech & Ravnkilde, 2004), particularly those with early onset and recurrent episodes of depression (Schmaal, Marquand, et al., 2015).

These findings are consistent with neurotrophic hypotheses of depression, which posit that abnormal subcortical development due to glucocorticoid abnormalities predate disease onset (Duman & Monteggia, 2006). In line with this, lower hippocampal volumes have been found in individuals with Cushing's syndrome (see Andela et al., 2015), those at high risk of developing depression (Amico et al., 2011), and seem to be particularly evident in at-risk and patient groups who have experienced adverse life events during childhood (see Frodl & O'Keane, 2013).

Grey matter atrophy and reduced white matter integrity have furthermore been linked with (and in some cases, predicted) poor clinical outcome in depression such as higher rates of relapse, prolonged chronicity, and lesser response to antidepressant treatments (Frodl et al., 2008; M. L. Murphy & Frodl, 2011). Conversely, normalisation of hippocampal volume (Ahdidan et al., 2011), and increased volume in other regions including the inferior frontal cortex and fusiform gyrus (Lai & Hsu, 2011) have been linked to remission and successful treatment. Although direct links with glucocorticoid mechanisms remain largely unexplored in patient samples, it is feasible that glucocorticoid neurodegenerative and neurogenic processes, particularly in subcortical areas, may play an aetiological role in structural alterations associated with disease progression (Campbell & Macqueen, 2004; Lupien, 1998; Pittenger & Duman, 2008) and treatment response (Santarelli et al., 2003).

1.4.2. Memory & Cognition

1.4.2.1. Glucocorticoid effects on hippocampal memory

In line with physiological changes, a vast amount of evidence exists for cortisol altering functional and behavioural processes, particularly those mediated by the hippocampus and amygdala, and areas of the midbrain and prefrontal cortex (Arnone et al., 2012; Savitz & Drevets, 2009). In particular, glucocorticoid modulation of the complex processes of declarative memory encoding, consolidation, storage, and retrieval has been extensively studied (McGaugh, 2000; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016). These processes are dependent on the medial temporal lobe (Schacter & Wagner, 1999; Squire &

Zola-Morgan, 1991), and glucocorticoid manipulations have yielded reliable evidence of alterations in hippocampal memory in humans and animals (De Kloet et al., 2008; de Quervain, Aerni, Schelling, & Roozendaal, 2009; Erickson et al., 2003; Lupien, 1998; van Stegeren, 2009).

While acute manipulations of cortisol may lead to improved or impaired memory depending on methodological and contextual factors, studies of prolonged elevations in glucocorticoids have mostly revealed detrimental effects on hippocampal memory (Conrad, 2010; Schwabe, Dalm, Schächinger, & Oitzl, 2008), confirming neurotoxic effects in line with structural damage. In humans, long-term increases in cortisol due to medical or experimental administration of exogenous glucocorticoids manipulation) are associated with declarative and visuo-spatial memory deficits (Brown & Chandler, 2001; Newcomer et al., 1999; Wolkowitz et al., 2009; A. H. Young, Sahakian, Robbins, & Cowen, 1999). These findings are corroborated by findings of cognitive impairments, decreased learning, and poorer declarative memory in patients with hypercortisolaemia due to Cushing's syndrome (Andela et al., 2015; Starkman et al., 1992; Starkman, Giordani, Berent, Schork, & Schteingart, 2001), with impairments sometimes linked to smaller hippocampal volumes (Starkman et al., 1992).

Effects of cortisol on memory were long considered puzzling due to seemingly opposing effects of glucocorticoids, with both improvements and impairments found following glucocorticoid administration (see Schwabe, Joëls, et al., 2012; Schwabe & Wolf, 2013; Wolf et al., 2016). Recent experiments have elegantly started to explain these effects, showing that glucocorticoids can have either beneficial or detrimental effects on stages of memory dependent on the timing of corticosteroid manipulation and the associated time course of action (Joëls, Pasricha, & Karst, 2013). According to these models, increased HPA axis activity shortly prior, during, or immediately after the learning of novel stimuli may lead to enhanced performance, thought to be due rapid stress-related glucocorticoid and noradrenergic actions facilitating attentional and encoding processes. Conversely, stress encountered a considerable time before learning can lead to impairing effects, due to glucocorticoid suppression of information processing unrelated to the stressful event (Schwabe, Joëls, et al., 2012). At the core of reconciling these findings lies an

improved understanding of the time course of cortisol effects, with performance differentially altered depending on rapid versus sustained modulation (Joëls, Fernandez, & Roozendaal, 2011; Joëls et al., 2013; Joëls, Sarabdjitsingh, & Karst, 2012). While single-dose studies are starting to provide compelling insight into these complexities, largely by modulating the stage of processing at which cortisol is introduced, the evidence for longer-term cortisol effects, providing additional understanding of cumulative effects over time, is only slowly starting to emerge (Brown, 2009; Brown et al., 2013; Brown, Vera, Frol, Woolston, & Johnson, 2007).

1.4.2.2. Glucocorticoid effects on cognition

Although cortisol's effects on declarative memory are most extensively studied, glucocorticoid effects on cognition extend beyond temporal regions, most notably to functions associated with areas of the PFC, where GRs and MRs are widely distributed (McKlveen et al., 2013). Working memory is a particularly well-studied function of PFC, and its alterations by stress manipulations appear to be distinct from the declarative memory effects discussed above (Lupien, 1998; Lupien, Gillin, & Hauger, 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Lupien et al., 2009; Zobel et al., 2004). These types of memory have different neural signatures, with declarative memory generally increasing use of hippocampal resources, and working memory increasing PFC (Arnsten, 2009, 2015) and parietal cortex activity with a concomitant decrease in hippocampal activity (Symonds et al., 2012). While both improvements and impairments in working memory have been found following acute cortisol administration depending on task characteristics (Luethi, 2008; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006; Porcelli et al., 2008; Schoofs, Preuß, & Wolf, 2008; Stauble, Thompson, & Morgan, 2013; Yuen et al., 2011), studies of tasks requiring further frontal lobe function, such as strategy use, have largely found impairments following increases in cortisol (Arnsten, 2015; Newcomer et al., 1999; A. H. Young et al., 1999).

1.4.2.3. Glucocorticoid effects on the amygdala

When material contains emotional salience, stress appears to confer predominantly enhancing effects on declarative hippocampal memory (Desmedt, Marighetto, Richter-Levin, & Calandreau, 2015; Erickson et al., 2003; Joëls et al., 2011; Wolf, 2008), an improvement that goes beyond the

preferential processing of emotionally salient stimuli evident under baseline conditions (Abercrombie et al., 2011; Buchanan & Lovallo, 2001; McGaugh, 2000). Findings from PFC-based tasks have been more mixed, although cortisol effects are generally stronger on tasks containing an emotionally relevant component (Luethi, 2008; McKlveen et al., 2013; Oei, Tollenaar, Spinhoven, & Elzinga, 2009). Such additional emotion-modulated stress effects on task performance are thought to be largely mediated by direct glucocorticoid and interacting noradrenergic effects on the basolateral amygdala (Adolphs, Cahill, Schul, & Babinsky, 1997; B. Roozendaal, Okuda, de Quervain, & McGaugh, 2006)(Adolphs et al., 1997) and its modulatory influences on the MTL, basal ganglia, and medial and orbitofrontal PFC (Erickson et al., 2003; Hermans et al., 2014; L. Kilpatrick & Cahill, 2003; Lupien et al., 2007).

1.4.2.4. Summary

In addition to differences in glucocorticoid kinetic properties and dosing, contextual and task-specific methodological factors and associated differences in neural loci are thought to mediate mixed findings of cortisol effects on memory long found in the literature. Finally, cortisol effects vary depending on the nature of the stimuli and the study population (de Quervain et al., 2009). These factors are all thought to influence the GR/MR occupancy achieved, which in turn is dependent on both the response to a stressor or absolute dose of glucocorticoids administered, and the basal levels prior to the manipulation (Dorey, Piérard, Chauveau, David, & Béracochéa, 2012; Joëls et al., 2011). These factors highlight the complexity that play a role in determining behavioural outcomes, and delineating the exact nature of how sustained HPA axis alterations impact memory functions remains a fruitful area of investigation.

1.4.2.5. Clinical evidence

Altered memory and cognitive performance are core behavioural symptoms of depressive disorders and accompany a range of other psychiatric diseases. In MDD, memory deficits, in particular, biases towards increased recollection of negative material and poorer specificity of autobiographical memory (Barnhofer et al., 2005; Hamilton & Gotlib, 2008; K. D. Young et al., 2012), are thought to be of theoretical importance for understanding symptomatology (Harmer,

2010). Memory and decision-making impairments have been related to disease severity (K. D. Young, Siegle, Bodurka, & Drevets, 2016) and risk status such as a family history of depression (Mannie et al., 2008; K. D. Young, Bellgowan, Bodurka, & Drevets, 2013), but further evidence is needed to clarify their specificity and association with neurochemicals and disease time course.

The PFC is crucial in understanding the aetiology, symptomatology, and recovery from psychiatric disorders (Carlson, Depetro, Maxwell, Harmon-Jones, & Hajcak, 2015; Drevets, 1999; Heinzel, Northoff, Boeker, Boesiger, & Grimm, 2010) thought to be partially due to its ability to control and modulate limbic and striatal brain areas (Bennett, 2011; Drevets, 1999; Heinzel et al., 2010; Willeumier, Taylor, & Amen, 2011). Findings of reduced down-regulation of these processes in stress-related disorders, and specifically, impairments in the executive functions it subserves (such as planning, strategy selection, and working memory) have been found in at least a subset of psychiatric disorders, such as depression (Garrett et al., 2014; Gohier et al., 2009; Heinzel et al., 2010; Kerestes et al., 2012; Maalouf et al., 2010).

Functional alterations in memory and cognition following glucocorticoids and associated neural changes are highly consistent with those found in psychiatric disease (Conrad, 2008; Erickson et al., 2003; Joëls, 2011; McEwen, 2003). Memory impairments and structural alterations seen in depressed individuals are at least partially linked to abnormal glucocorticoid functioning (Abercrombie et al., 2011; Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004; Correa et al., 2012; Fairhall, Sharma, Magnusson, & Murphy, 2010; Vythilingam et al., 2004). Clinical findings and cortisol effects especially overlap in altered declarative memory of verbal stimuli, with some studies associating acute cortisol increases with improved recall (Nater et al., 2007), but repeated exogenous glucocorticoids leading to impaired performance (Brown et al., 2004, 2013; Brown & Chandler, 2001). Nevertheless, reports that link glucocorticoid-induced hippocampal deficits, memory performance, and HPA axis functioning in depression remain sparse, leaving the precise links with disease progression and cortisol status to be elucidated (Moylan, Maes, Wray, & Berk, 2012). In contrast, a direct link between functional deficits in emotional memory processing, particularly fear conditioning, and PTSD symptomatology following traumatic events and their

modulation by abnormal cortisol and noradrenaline levels has been found (de Quervain et al., 2009).

1.4.3. Emotional attention, perception, recognition

1.4.3.1. Glucocorticoids in emotional processing

Acute stress is associated with the promotion of focused attention, alertness, and vigilance to, and encoding of, emotionally salient and threatening stimuli (Joëls et al., 2007). Short-term increases in cortisol, tested following stress and/or pharmacological interventions, have been shown to modulate at least a subset of these affective processes (F. S. Chen, Schmitz, Domes, Tuschen-Caffier, & Heinrichs, 2014; Ellenbogen, Schwartzman, Stewart, & Walker, 2002, 2006; Erickson et al., 2003; Putman & Roelofs, 2011), such as attentional resource allocation towards negative material and social threat (Dolcos, 2014; Putman, Hermans, Koppeschaar, van Schijndel, & van Honk, 2007; Putman, Hermans, & van Honk, 2010; Roelofs, Bakvis, Hermans, van Pelt, & van Honk, 2007). Furthermore, studies indicate that acute stress rapidly enhances the processing of emotional faces, and endogenous cortisol levels in healthy controls have been linked with preferential processing of emotional faces, and a higher tendency to judge neutral faces as emotional (F. S. Chen et al., 2014; Feeney, Gaffney, & O'Mara, 2012). Cortisol has been shown to play an important role in social aggression in animals and contribute to normal social functioning in humans (Bertsch, Böhnke, Kruk, Richter, & Naumann, 2011; Henckens, Klumpers, et al., 2015; Sapolsky, 1995, 2004), and emotional facial expressions constitute particularly salient biological stimuli with important communicative functions, such as providing indications of the intensity and valence of social interactions (for example, levels of threat or pleasure; Calder & Young, 2005; Critchley et al., 2000; Van Honk et al., 2003).

One previous study has provided evidence from repeated pharmacological cortisol manipulations on facial expression tasks. When administered orally at 25mg per day for 4 days, hydrocortisone was found to decrease neural activity in the subgenual anterior cingulate cortex (ACC) evoked by sad faces in healthy males, with no alterations in response to happy or neutral stimuli (Sudheimer et

al., 2012). Furthermore, patients with Cushing's disease (endogenous hypercortisolaemia) showed increased subcortical activation and lower recognition accuracies for negative emotional expressions (Langenecker et al., 2012). Evidence in both patient and healthy populations thus suggests that glucocorticoid fluctuations alter the neural reactivity to and interpretation of negative face stimuli, but evidence remains inconclusive regarding the specificity of negative emotions, and associated emotion discrimination ability in different populations (cf. Kober et al., 2008).

1.4.3.2. Clinical evidence

Patients with depressive and anxiety disorders show an increased tendency to perceive and interpret stimuli as more negative compared with healthy volunteers (Elliott et al., 2011; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Hamilton & Gotlib, 2008; Harmer, 2010). These effects have been found for different types of stimuli, including negative words, pictures, and faces (Sheline, 2003; Surguladze et al., 2004, 2005, 2010; Victor, Furey, Fromm, Öhman, & Drevets, 2010). As discussed above, emotional processing biases appear to be useful markers of pathological states, vulnerability, and treatment efficacy (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Walsh & Harmer, 2015; Warren, Pringle, & Harmer, 2015a) and some biases – such as alterations in amygdala reactivity and fear processing – have been found across several disorders (Kret & Ploeger, 2015). In particular, altered perception and recognition of emotional facial expressions have been found in a variety of psychiatric disorders (Bortolon, Capdevielle, & Raffard, 2015; Bourke, Douglas, & Porter, 2010; Gur et al., 2002; D. J. Holt et al., 2006; Leppänen, 2006; Staugaard, 2010; Surguladze et al., 2004, 2005) and appear to be highly sensitive markers of psychiatric disease status and risk (Bourke et al., 2010; Felmingham, Bryant, & Gordon, 2003). Patients with depression have often been found to show increased processing of negative (sad and angry) faces (Bourke et al., 2010), while anxiety, particularly social anxiety, is strongly associated with the abnormal processing of threat-related (fearful and angry) face stimuli (Bradley, Mogg, Falla, & Hamilton, 1998; Staugaard, 2010). However, despite a general agreement that glucocorticoid mechanisms may contribute to mood pathologies through activation of

extrahypothalamic regions (Erickson et al., 2003), there is little direct evidence from non-acute cortisol manipulations on the modulation of emotional processing (Cowen, 2009; Joëls, 2011).

1.4.4. Networks & functional connectivity

1.4.4.1. Glucocorticoid effects on functional connectivity

Overall the brain areas that are most strongly implicated in affective disorders and the altered processing reviewed here, such as the hippocampus, amygdala and medial prefrontal cortex, also express high levels of glucocorticoid receptors and are key targets for manipulations of cortisol. Crucially, changes in affective and cognitive biases are often linked to interactions between these areas at any given point, and differences in their (functional) coupling may provide behaviourally and clinically relevant insights (Bennett, 2011; Herman et al., 2005; Jankord & Herman, 2008; Urry, 2006).

Research using functional magnetic resonance imaging (fMRI) has provided insight into the functional architecture of the brain during or immediately after stress, both while performing tasks and while "at rest", i.e. not focussing on a particular task. Measures of neural processes while at rest provide us with insight into (emerging) stable networks of connectivity between areas showing co-activation related to "baseline" neural activity (e.g. Damoiseaux et al., 2006). Acute stress has been shown to rapidly alter resting-state functional connectivity (rsFC) between the amygdala and a number of brain regions, including the medial PFC, ACC, insula (Quaedflieg et al., 2015; Soares, Sampaio, Ferreira, et al., 2013; van Marle, Hermans, Qin, & Fernández, 2010), and resting-state connectivity has associated with endogenous HPA axis status (Kiem et al., 2013). Studies have shown differences in baseline brain activity related to cortisol increases, mediated by the medial temporal lobe, limbic system, and thalamus (Hall, Moda, & Liston, 2015). Cortisol and HPA axis status have been linked to connectivity strength, in particular between the medial temporal lobe and limbic areas, and - to a lesser degree - prefrontal and cingulate cortex, and there is evidence for large-scale stress-induced alterations in rodents (Henckens, van der Marel, et al., 2015). Fewer studies have investigated rsFC following non-acute alterations of the HPA axis, but repeated

environmental stress in healthy populations has been associated with altered frontal and attentional rsFC (Soares, Sampaio, Ferreira, et al., 2013; Soares, Sampaio, Marques, et al., 2013), mirroring functional connectivity changes following similar stressors during task performance in healthy individuals (Liston, McEwen, & Casey, 2009).

1.4.4.2. Clinical evidence

rsFC changes found in psychiatric populations to some extent mirror the alterations found in task-based fMRI studies. In depression, widespread effects have been found particularly in validated connectivity patterns including the default mode (DMN; Broyd et al., 2009a; Greicius, Krasnow, Reiss, & Menon, 2003), salience (SN; Pannekoek et al., 2014), and executive control (CEN; Greicius et al., 2007; Salomons et al., 2014; Veer et al., 2010) networks. Altered rsFC patterns in both depression (reviewed in Dichter, Gibbs, & Smoski, 2015; Greicius et al., 2007; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015) and anxiety further converge on abnormal connectivity of the amygdala (Baur, Hänggi, Langer, & Jäncke, 2013; Bebko et al., 2015; M. Li et al., 2015), including decreased amygdala connectivity with the anterior cingulate (Anand, Li, Wang, Lowe, & Dzemidzic, 2009; Greicius et al., 2007), insula (Baur et al., 2013; Pannekoek et al., 2014; Veer et al., 2010), and areas of the PFC (Greicius et al., 2007; Hahn et al., 2011). Initial studies suggest that rsFC profiles and their alterations over time may have the potential to give insight into clinical symptom progression and treatment outcomes (Etkin ea 2009, Fox ea 2012, Liston ea 2014, Salomons ea 2014 – see Hall ea 2015, Dichter ea 2016).

The areas of resting-state connectivity related to psychiatric disorders partially overlap with those of stress-related functional connectivity, and altered HPA axis activity has been posited to contribute to psychiatric resting-state connectivity abnormalities (see Hall et al., 2015 for a review). Vulnerability-associated alterations in rsFC patterns, in particular reductions in rsFC between the amygdala and areas such as the insula, medial temporal lobe, and ACChave been found at different developmental time points. Research on early life stress and other risk factors appear to confirm the role of the amygdala as a critical mediator of wider rsFC responses to changes in the central stress circuitry (e.g. Pagliaccio et al., 2015). These studies provide an intriguing longitudinal perspective

of the potential stratification of differential developments, particularly in rsFC involving brain areas functionally associated with cognitive control, salience processing, and learning mechanisms. As with task-based effects, promising studies on glucocorticoid ultradian rhythms and the time course of recovery post-stress are – while likely crucial in understanding network effects – still in their infancy (Soares, Sampaio, Marques, et al., 2013; Vaisvaser et al., 2013; Veer et al., 2011; Vogel et al., 2014).

1.4.5. Summary

To summarise, cortisol is known to affect learning and memory processes via genomic and non-genomic effects at GR/MR, changes in synaptic plasticity, and altered neurogenesis (for comprehensive reviews, see Finsterwald & Alberini, 2014; Joëls et al., 2011). Direct and modulatory influences of altered glucocorticoid effects in the MTL, PFC, and amygdala are thought to be key factors in these functional alterations (Arnone et al., 2012; Savitz & Drevets, 2009), and the exact nature of these effects appear to depend upon dose and duration of treatments, individual differences in cortisol diurnal rhythms, and stimulus properties such as valence (Cunningham-Bussel et al., 2009; Tops, 2003). The neural substrates most strongly impacted by cortisol partially overlap with those underlying emotional processing abnormalities seen in depressive and anxiety disorders (Erickson et al., 2003; Hall et al., 2015; Kemp & Felmingham, 2008; Price & Drevets, 2012). Importantly, behavioural and corresponding neural processes are being delineated with increasing specificity, allowing the refinement of mechanistic disease and treatment models and reinforcing the need to characterise understand the underlying neurochemical modulators. With regards to cortisol and psychiatric disorders, striking findings point to the importance of further refining our understanding of its modulatory effects, particularly with regards to more sustained changes in the activity of the HPA axis.

1.5. Rationale & research aims

1.5.1. Acute vs. sustained cortisol manipulations

The large body of experimental evidence in humans from acute or short-term interventions, altering HPA axis activity over a period of minutes to hours, provides crucial insight into the mechanisms of cortisol on the brain, but is of limited clinical relevance to understanding stress-related disorders. Conversely, the strong evidence base for an important role of the HPA axis in response to environmental challenges (as discussed above) provides clinically relevant findings but is largely unable to disentangle direct effects of cortisol from other (mal)adaptive systemic changes, and thus lacks a detailed characterisation of cortisol's complex neural-behavioural mechanisms. Crucially, the effects of non-acute, sustained exposure to glucocorticoids may differ from acute interventions due to cascading effects on neural circuits, altering brain functioning in regions beyond those containing GR/MR receptors (Dias-Ferreira et al., 2009; Holmes & Wellman, 2009; Moench, Maroun, Kavushansky, & Wellman, 2016; Radley et al., 2004; Radley, Morilak, Viau, & Campeau, 2015; Starkman, Giordani, Gebarski, & Schteingart, 2007; Szot et al., 2006).

Progress in characterising the effects of sustained cortisol abnormalities on neural and behavioural mechanisms is hindered by the methodological and ethical difficulties of studying changes in the HPA axis over long periods of time. Patients with disorders that show abnormal HPA axis function often form heterogeneous samples confounded by comorbidities, medication use, and complex medical histories, thus providing inconclusive evidence. As evidenced by long-term use of glucocorticoids as medication, disrupting the hormone levels and feedback mechanisms of the HPA axis for extended periods of time is both difficult and potentially dangerous due to severe side effects such as e.g. adrenal suppression. Only a limited number of studies have attempted to manipulate glucocorticoid levels over a periods of several days or weeks (Brown et al., 2013, 2015; McAllister-Williams. & Rugg, 2002; Sudheimer et al., 2012; A. H. Young et al., 1999). In addition to continued developments of direct glucocorticoid modulators, it is therefore of great interest that

recent developments show a potential role for manipulations of the gut microbiota and immune system to target the HPA axis and its stress-regulatory functions.

1.5.2. Research aims & thesis overview

The objective of this thesis is to delineate how sustained alterations of the HPA axis affect the processing of behavioural and neural processes relevant for understanding the development and maintenance of psychiatric, particularly depressive, symptoms. In two projects aiming to manipulate HPA axis functioning and cortisol levels in healthy participants non-acutely, we sought to clarify how cortisol contributes to cognitive and emotional biases and their neural correlates, subjective wellbeing, and functional neural connectivity. In order to address this question, we followed two complementary lines of investigation: firstly, to alter HPA axis functioning by directly manipulating glucocorticoid levels with pharmacological agents (*Study 1*); and secondly, by using a more exploratory approach, attempting to target the HPA axis indirectly through manipulations of gut microbiota (*Study 2*). A range of emotional and cognitive tasks was selected to assess behavioural and neural measures previously shown to be relevant for understanding the symptomatology of stress-related disorders such as depression and anxiety.

Study 1: To mimic some of the neural effects of prolonged exposure to elevated levels of cortisol and to identify neural substrates of chronic glucocorticoid administration, we completed a placebo-controlled study administering a 10-day course of 2 x 20mg hydrocortisone (exogenous cortisol) to healthy volunteers. On the final day of treatment, participants completed a behavioural and fMRI testing battery. Results from this study are described in Chapters 2-5:

- Chapter 2 outlines the methodology of the hydrocortisone study and provides the demographic and trait characteristics of the study sample. In addition to urinary free cortisol (UFC) levels before and after hydrocortisone administration, state measures of positive and negative affect, wellbeing, and subclinical psychiatric symptoms are discussed.

- Chapter 3 contains results from a number of memory tasks, namely, a neutral declarative memory paradigm performed during fMRI, and behavioural measures of emotional declarative memory and neutral working memory.
- Chapter 4 includes a range of emotional information processing tasks, focussing primarily on facial expression perception and recognition: namely, a facial expression perception task completed while undergoing fMRI, a behavioural facial expression recognition task, a continuous flash suppression task containing emotional faces, and an attentional dot-probe task containing valenced words.
- Chapter 5 discusses the results of two analyses performed on resting-state functional connectivity data: a model-free independent component analysis, and a hypothesis-driven seed-based analysis.

Study 2: To investigate the potential of altering HPA axis function via the gut microbiota, a placebo-controlled study administering a 21-day course of prebiotics to healthy volunteers was completed, with a behavioural testing battery administered at the end of the three weeks. Results from this study are discussed in Chapter 6:

- Chapter 6 contains results from a behavioural test battery assessing emotional information processing, in addition to measures of the cortisol awakening response (CAR), and subjective measures of mood and subclinical psychiatric symptoms.

CHAPTER 2: EFFECTS OF REPEATED HYDROCORTISONE ON SUBJECTIVE WELL-BEING AND URINARY FREE CORTISOL

2.1. Introduction

2.1.1. Sustained increases in cortisol

When administered as medications, exogenous glucocorticoids are often associated with symptoms of hypomania, anxiety, psychosis, and depression (as discussed in Chapter 1; Fardet et al., 2014; Naber et al., 1996; Rome & Braceland, 1952; The Boston Collaborative Drug Surveillance Program, 1972). Adverse effects associated with the use of corticosteroids are closely related to dose and duration of treatment (Judd et al., 2014). After oral corticosteroid therapy of one month or longer, the most severe of these effects include adrenal suppression and Cushingoid features, while at shorter treatment durations, side effects may already include mood and sleep disturbances, and altered immune responses, alertness, and energy levels (Judd et al., 2014; Starkman, 2013). These reports of persistent alterations in well-being and impaired psychological functioning, especially at high doses (Judd et al., 2014), point to the ability of altered glucocorticoid signalling to profoundly impair clinically relevant neural and behavioural processes. Nevertheless, exactly how cortisol influences the development of psychiatric symptoms over time remains unclear (Wolkowitz et al., 2009).

2.1.2. Intervention studies in healthy participants

Studies in healthy participants are particularly useful in providing evidence that is not confounded by disease status, and are vital to elucidating the mechanisms underlying the link between pharmacological action and psychological constructs. As outlined in the General Introduction, the majority of pharmacological challenge studies have investigated acute pharmacological challenge

and administration of glucocorticoids due to methodological difficulties associated with altering cortisol levels over days to weeks rather than hours. Despite the increasing detail with which many functional effects of acute cortisol have been characterised in healthy populations, our understanding of their link to psychiatric symptoms is thus limited by the predominance of short-term HPA axis manipulations and a relative scarcity of data from repeated glucocorticoid alterations and other non-acute HPA axis interventions.

A small number of studies have administered glucocorticoids repeatedly over a number of days to healthy volunteers in attempts to manipulate cortisol levels over a period of several days to weeks. One study, which administered 20 mg of hydrocortisone per day for 10 days but in male volunteers, did not report on side effects in their study sample of healthy young males (A. H. Young et al., 1999). Other studies have found no reliable effects of cortisol administration on subjective well-being (Brown et al., 2013, 2015; McAllister-Williams. & Rugg, 2002; Sudheimer et al., 2012), although some have reported adverse effects on quality of sleep and mild behavioural changes (A. H. Young, Sharpley, Campling, Hockney, & Cowen, 1994; see Wolkowitz et al., 2009). In addition to the lack of measures for subjective and subclinical psychiatric symptoms in some of these studies, inconsistencies in reporting measures may have led to potential alterations in subjective state being poorly captured, and further obscures our understanding of the impact of exogenous glucocorticoids on well-being in healthy volunteers.

2.1.3. Aims of this chapter

Given the relative scarcity of placebo-controlled experimental studies administering repeated doses of glucocorticoids over several days, we designed a pharmacological intervention study in healthy male and female volunteers who received either 20mg hydrocortisone (synthetic cortisol) or a placebo twice daily over a course of 10 days. The purpose of this study was to assess the impact of elevated cortisol levels on the behavioural and neural processing of emotional information and memory, and self-report measures of subjective affect and well-being, beyond findings from cortisol manipulations such as acute pharmacological and stress challenges and single-dose

glucocorticoid administration. The current chapter describes the subjective (self-reported affect and well-being) and endocrine measures delineating changes in mood and subclinical symptoms and supplementing the neural and behavioural outcome variables are described. Furthermore, it outlines the design and procedure of the sustained hydrocortisone challenge study, and presents the study sample characteristics. It thus provides the methodological background for the results presented in Chapters 3, 4, and 5.

2.2. Materials & Methods

2.2.1. Participants

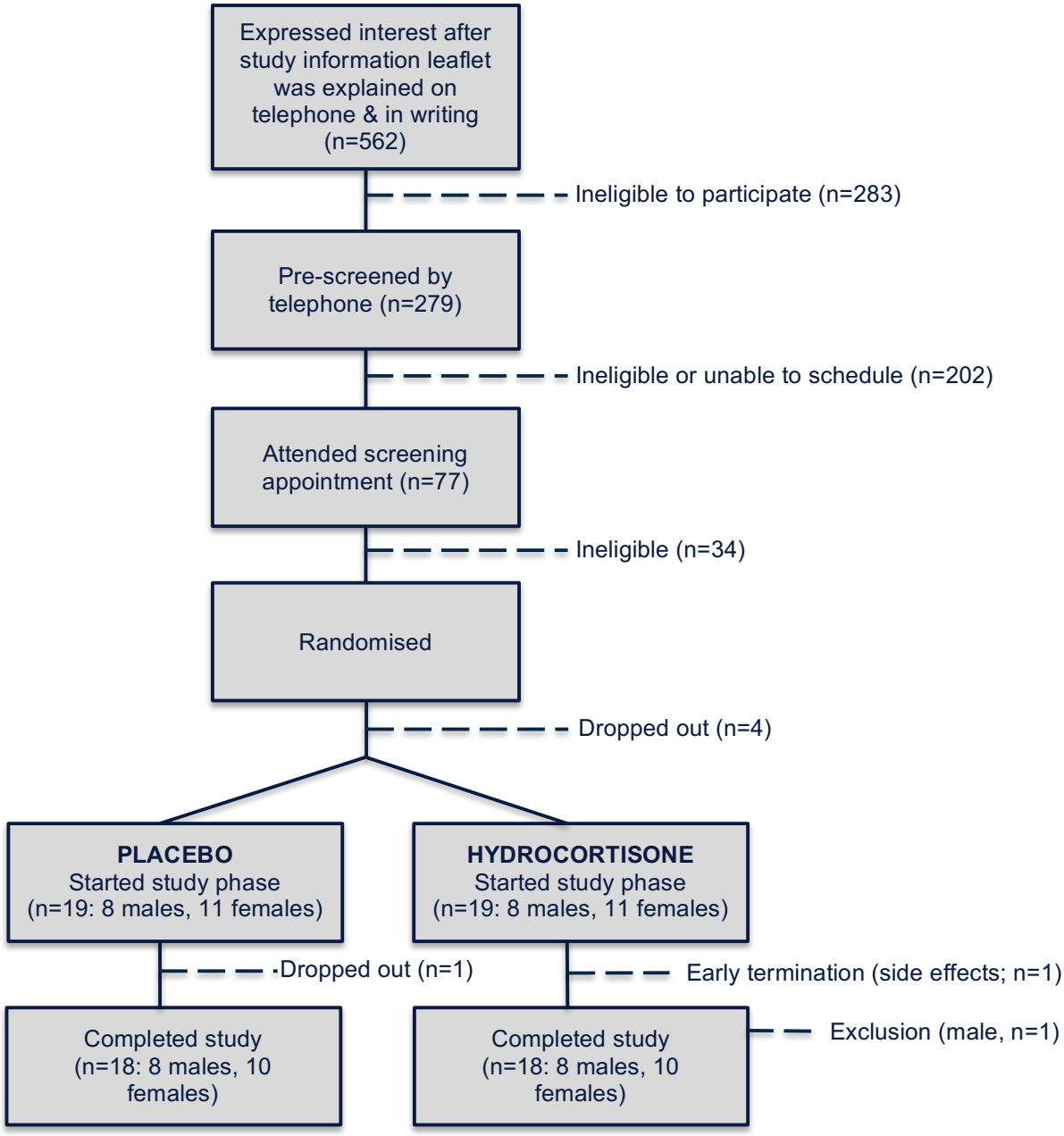
Participants were recruited via distribution of posters, web advertisements, and via e-mails to student bodies. Upon first contact, volunteers were sent an e-mail giving a brief description of the study, followed by a full briefing of study procedures and an initial eligibility screening via the telephone by the researcher. Participants were emailed with a full study information pack and – if eligible and interested – invited for a full screening appointment at the study site. A full list of eligibility criteria can be found in **Table 2-1**. Study protocols were approved by the NHS Research Ethics Committee (South Central – Oxford B, Reference 12/SC/0026).

Table 2-1. Inclusion and exclusion criteria for the hydrocortisone study

Category	Criteria
Demographics	**Inclusion:** Male / Female, 18-45 years of age, BMI of 18-30kg/m^2, Fluent in English, Willing / able to provide informed consent
MRI	**Inclusion:** Safely be able to undergo MRI scanning, Right-handed **Exclusions:** Pacemaker / pacing wire, Implanted devices containing metal, Previous brain surgery, Large tattoos or piercings that cannot be removed, Claustrophobia
Demographics	**Exclusion:** Irregular sleep / wake rhythm (e.g. regular nightshifts), Participation in study administering medicine in past 6 weeks, Previous participation in study using the same computerized tests, Pregnant / breast-feeding
Psychiatric history	**Exclusion:** Any current or previous psychiatric disease (as assessed by self-report and the SCID), any psychiatric disease (mood disorders) in a first-degree family member, History of drug / alcohol dependence or severe abuse, History of illicit drug use within three months
Medical history	**Exclusion:** Neurological disease, Epilepsy, Myasthenia gravic, Endocrine

	disease, Hyper-/hypothyroidism, Clinically significant hepatic, cardiac, obstructive, respiratory, renal, cerebrovascular, metabolic, or pulmonary disease, Gastrointestinal obstruction, Ulcerative colitis, Heart / blood vessel disease.
Contraindications to hydrocortisone	**Exclusion:** Significant medical history in self or first-degree family member involving Diabetes mellitus, or Glaucoma (or first-degree family history of glaucoma). Significant medical history in self involving Hypertension, Liver disease, Epilepsy, Osteoporosis, Peptic ulceration, Asthma or any other significant allergic condition, Renal insufficiency, Tuberculosis, any current active infection or immunisation within the last three months.

Figure 2-1. Flow chart of recruitment & participant numbers



The number of people who were contacted, screened, and included in the study is shown in **Figure 2-1**. Of the 37 participants who completed the study, one participant was excluded due to an abnormal finding in the MRI scan, leading to a total of 36 participants (16 male, 20 female) aged 18-45.

2.2.2. Design & Procedures

The study was designed as a double-blind, placebo-controlled, parallel group pharmacological intervention study. Following 20 doses of either 20mg hydrocortisone or placebo capsules, participants completed a battery of measures including computerised tasks assessing memory and emotional processing (described in Chapters 3 and 4), fMRI (described in Chapters 3-5), and measures of mood and affect (current chapter).

2.2.2.1. Recruitment & Screening

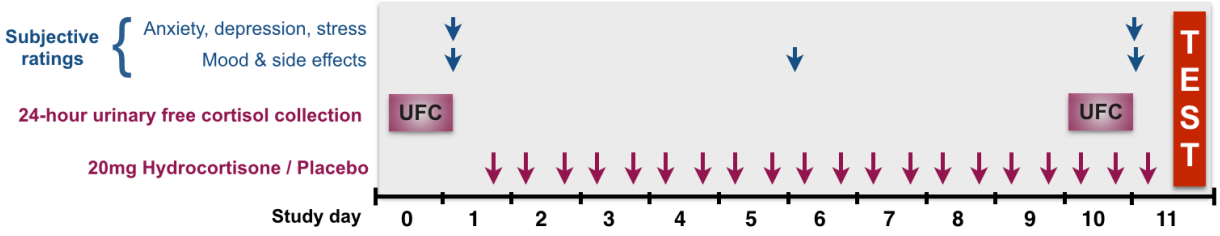
Upon making contact with the research team, participants were sent an information booklet and asked to provide contact details in order for a full briefing and pre-screening by the researcher via telephone. Individuals who were eligible and willing to participate were scheduled for an initial screening appointment (procedures outlined below).

Participants attended a 1-1.5 hour screening appointment prior to scheduling the pharmacological intervention. The researcher briefed participants on the details of the study procedures, gave the opportunity to ask questions, and acquired written informed consent. Participants were then asked to provide their age, sex, education level, alcohol and caffeine intake, nicotine use, and use of regular medication and contraceptives, before being screened for current or previous psychiatric disease and substance abuse / dependence using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1997), any relevant medical history, and contraindications to hydrocortisone treatment and MRI scanning. Further, participants underwent a physical screening by a qualified medical doctor. If eligible, participants then completed measures of verbal IQ (administered by the researcher), life events, and self-report trait questionnaires (as detailed below).

2.2.2.2. Treatment phase

Participants completed the study phase involving ingestion of placebo / hydrocortisone in their own homes while continuing with their normal routines. For an overview of the study phase, please see **Figure 2-2**. Participants were asked to collect all urine they passed for 24 hours as a baseline measure of UFC on the day prior to the start of drug / placebo administration (i.e. from waking on "day 0" until waking on "day 1", with the intake of the first capsule scheduled for the evening of day 1). Within 24 hours of completion, of the urine collection, participants dropped the sample off at the study site for analysis by the researcher, at which point participants also collected their medication / placebo capsules.

Figure 2-2. Timeline of main treatment phase: hydrocortisone ingestion, urinary cortisol measurements, and self-report questionnaires.



During the main treatment phase participants ingested a total of 20 capsules of either placebo (lactose powder) or hydrocortisone (20mg), starting on the evening of day 1, and then taking capsules twice daily (morning and evening) until the morning of the final testing day (Day 11, ingested at least 2 hours before the start of the final appointment in order to minimise rapid effects of hydrocortisone post-ingestion). The capsules were scheduled to be ingested at fixed times (adjusted to be within 2 hours of waking and about 10-12 hours thereafter, depending on participants' routines), at which point participants were also asked to record intake times and any potentially relevant comments they had. For 24 hours before their scheduled waking time on the final testing appointment day (Day11), participants again collected their urine to allow measurement of urinary free cortisol at the end of the pharmacological intervention. On the first and last days of the study phase, participants completed measures of perceived stress, state anxiety, and subclinical symptoms of depression. Measures of state affect and mood and a brief

questionnaire designed to capture any side effects were completed at the same times, and additionally at the midpoint of the treatment phase (see details below).

The study phase was scheduled to be at a time during which participants were not expecting to undergo any external stressors or irregular sleep schedules (e.g. work deadlines, exams / exam preparations, or competitions). Completion of daily logs confirmed that no participants had experienced any unexpected life stressors during the study phase. Furthermore, participants were asked to limit their alcohol intake (no alcohol during urinary free cortisol collection, or for 24 hours prior to the final appointment, and a maximum of 4 units per day, although encouraged to abstain, for the rest of the study), limit their caffeine intake to 1 caffeinated drink prior to testing on the final day, and refrain from taking any other medication (except oral contraceptives) throughout the study phase and one week prior unless agreed with the study team.

Final testing appointment

Participants were asked to have a large snack before attending the final appointment, and were then asked to refrain from smoking, drinking caffeine, or eating until the end of the appointment, except for an allowance of one cup of tea and a small lunch after the MRI appointment. All appointments were scheduled to start at or as soon after 12 noon as possible in order to standardise the effects of circadian cortisol activity and complete testing during the declining circadian phase in the afternoon. The final testing appointment took place at the Oxford Centre for Magnetic Resonance Imaging (OCMR, John Radcliffe Hospital) and the University of Oxford (Department of Psychiatry, Warneford Hospital) and lasted approximately 5 hours in total.

Upon arrival at the study site, participants were briefed on the MRI procedures and provided informed consent for MRI scanning. At the start of, twice during, and again at the end of the appointment, participants rated their mood. After completion of the initial mood ratings and a pre-scan encoding task for a memory paradigm described below, participants underwent MRI scanning consisting of a resting state scan, 2 computerised tasks, a perfusion scan, and approximately 10 minutes of supplementary scans.

Following completion of the MRI appointment, participants had a short break before continuing their appointment at the Department of Psychiatry to complete the behavioural test battery. Specifically, this consisted of the Emotional Test Battery (ETB; Harmer, O'Sullivan, et al., 2009; Harmer, Goodwin, et al., 2009; Harmer, Shelley, Cowen, & Goodwin, 2004), which is a validated computerised test battery assessing the processing of emotional stimuli that includes a facial emotion categoriisation task, an emotional memory task, and a dot-probe task with valenced words. Furthermore, participants were asked to complete an emotion-potentiated startle task, a continuous flash suppression task using emotional faces, a visual n-back working memory task, and a declarative list-learning task, which have been established as measures of emotional and cognitive processing sensitive to pharmacological interventions. Full details of the relevant task and MRI parameters can be found in Chapters 3-5.

Following completion of all behavioural and questionnaire measures, participants were asked to report any side effects or difficulties they experienced during the study phase, and to indicate which treatment they thought they had received (hydrocortisone or placebo). Finally, they were given the opportunity to ask questions, and able to find out (from a researcher not involved in the study) whether they had received the active (hydrocortisone) or placebo capsules.

2.2.3. Materials

2.2.3.1. Cortisol manipulation & assessment

Hydrocortisone administration

Hydrocortisone is the synthesised form of cortisol, and is widely used as a medication. We administered 20mg in the morning and 20mg in the evening, in order to ensure a stable increase in basal cortisol levels and to mimic evening excess secretion previously found in a sub-set of depressed patients (Stetler & Miller, 2011). A dose of 40mg hydrocortisone per day for ten days was not expected to result in adrenal suppression (or lessened adrenal function following cessation) based on similar study protocols, which have previously reported minimal side effects in healthy males (McAllister-Williams. & Rugg, 2002; A. H. Young et al., 1999). To minimise the likelihood

of participants experiencing serious adverse events, and to maintain a homogeneous study sample, our exclusion criteria were aimed to include only participants with no significant medical history.

Blinding & randomisation

The placebo (lactose) powder and tablets of (20mg) hydrocortisone were encapsulated by external pharmacy services (Cardiff & Vale University Health Board, St Mary's Pharmaceutical Unit; Cardiff, UK) and a qualified researcher at the study site packaged the blinded treatment materials according to a randomisation schedule. Participant numbers were pseudo-randomised to allow early termination of the study after multiples of 8 participants and stratified for gender.

Urinary free cortisol

Participants were verbally briefed on and received written instructions for the completion of the 24-hour urine collection for the analysis of UFC. The instructions specified how to achieve the most accurate results for the study by adjusting waking times on the days of collection, the importance of collecting all urine passed within the 24 hours, and details for storage. Participants were provided with urine collection cups and sterile plastic containers.

2.2.3.2. Semi-structured interviews & questionnaires

Participants were screened for current or previous psychiatric disease and substance abuse / dependence using the Structured Clinical Interview for DSM-IV Axis I Disorders (Goodyer, Herbert, Tamplin, Secher, & Pearson, 1997). In order to assess number of stressful life events, the Life Events Rating Scale (LERS; Goodyer et al., 1997) was administered. Additionally, participants completed self-report trait questionnaires of personality (Eysenck Personality Questionnaire, EPQ; Eysenck & Eysenck, 1975), anxiety (Spielberger State-Trait Anxiety Inventory - Trait, STAI; Spielberger, Gorsuch, & Lushene, 1970), and perceived stress responsivity (Perceived Stress Responsivity Scale, PSRS; Schlotz, Yim, Zoccola, Jansen, & Schulz, 2011). The National Adult Reading Test (NART; H. Nelson, 1982) was administered in order to estimate participants' verbal IQ. In order to assess variation in well-being at different time points in the study, participants completed measures of depression (Beck Depression Inventory, BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), anxiety (Spielberger State-Trait Anxiety Inventory -

State, STAI-S; Spielberger et al., 1970), perceived stress (Perceived Stress Scale, PSS; Cohen, Kamarck, & Mermelstein, 1983), and mood (Visual Analog Scales [VAS], Bond & Lader, 1974; Befindlichkeitsskala [BFS], von Zerssen, Strian, & Schwarz, 1974; and Positive and Negative Affect Schedules [PANAS], Watson, Clark, & Tellegen, 1988).

2.2.3.3. MRI protocol

Magnetic resonance images were collected on a 3 Tesla Siemens MAGNETOM Trio system at the University of Oxford, Centre for Clinical Magnetic Resonance Research (OCMR), using a 32-channel head matrix coil (Siemens, Erlangen, Germany). The duration of the final neuroimaging protocol was 55-60 minutes and consisted of anatomical and functional sequences**.** Prior to functional imaging, high-resolution T1-weighted structural images (repetition time [TR] = 2040ms, echo time [TE] = 4.72ms, field of view = 232mm, flip angle = 8°, voxel dimension = 0.9 x 0.9 x 0.8mm, acquisition time = 7 min 6 s), and field map images to correct for magnetic field inhomogeneities (TR = 488ms, TE 1 = 5.19ms, TE 2 = 7.65, field of view = 224mm, flip angle = 60°, voxel dimension = 3.5 x 3.5 x 3.5 mm, acquisition time = 1min 3s) were acquired. This was followed by a resting-state scan, and two functional EPI sequences during a memory encoding and facial expression task, as described in detail in Chapters 3-5.

2.2.4. Data Analysis

2.2.4.1. Urinary free cortisol (UFC)

The 24-hour urine sample was measured by weight and ~20cl was decanted for freezing at -20° C. Samples were transported on dry ice by courier for analysis by the St James' University Hospital Endocrinology Laboratory (Leeds, UK), and analysed using liquid chromatography linked to tandem mass spectrometry for levels of UFC (Wood et al., 2008). In addition to absolute UFC levels, the relative increase in UFC from baseline to post-treatment was calculated.

2.2.4.2. Demographics & questionnaires

Demographic and questionnaire values were analysed in SPSS (version 22.0; IBM) using one-way analysis of variance (ANOVA) with treatment group and gender as factors. Questionnaires were

analysed using split-plot ANOVAs with treatment group and sex as between-subjects factors, and day of completion as a within-subject factor for questionnaires repeated more than once. Pairwise follow-up tests were Sidak-corrected for multiple comparisons.

2.3. Results

2.3.1. Demographics & trait measures

Demographic and trait variables for the placebo and hydrocortisone groups are shown with their p-values from the respective ANOVA group effects in **Table 2-2**. Groups were well-matched on all education and trait measures, with the exception of EPQ-neuroticism. Males in the hydrocortisone group showed lower EPQ-neuroticism scores than males in the placebo group. In the final sample of 36 participants, highest completed education levels were matched between groups: 5 participants had completed a postgraduate degree (3 in cortisol group), 18 had completed an undergraduate degree (9 in the cortisol group), and 13 participants had completed high school (6 in the cortisol group). Of the 20 females, 14 were using hormonal contraceptives (implant or oral; 9 in the placebo group, 5 in the cortisol group).

Table 2-2. Demographic information and self-reported scores on trait questionnaires

	Placebo	Hydrocortisone	Group effect (p)
Age in years	24.00 (6.62)	23.78 (4.72)	*p=0.91*
Perceived Stress Reactivity Scale	16.67 (5.46)	15.18 (5.63)	*p=0.43*
Spielberger Anxiety Inventory-Trait	34.06 (5.37)	32.22 (5.33)	*p=0.31*
EPQ- Extroversion	15.39 (4.15)	14.56 (3.52)	*p=0.52*
EPQ- Neuroticism	7.94 (4.67)	4.50 (3.09)	*p=0.013**
EPQ- Psychoticism	3.22 (2.13)	2.78 (2.60)	*p=0.58*
EPQ-Lieing	6.72 (4.35)	7.06 (4.15)	*p=0.82*
Alcohol (units per week)	9.89 (9.81)	7.78 (5.64)	*p=0.43*
Caffeine (units per day)	2.94 (2.39)	2.50 (0.92)	*p=0.47*
Nicotine (cigarettes per week)	0.11 (0.47)	0.72 (2.42)	*p=0.30*
National Adult Reading Test	115.01 (6.68)	117.72 (5.65)	*p=0.20*
Number of participants who completed postgraduate (PG), undergraduate (UG), high school (HS) education	PG UG HS 2 9 7	PG UG HS 3 9 6	n/a

2.3.2. Urinary free cortisol

UFC levels assessed by 24-hour urine collection prior to and at the end of hydrocortisone/placebo administration are shown in **Table 2-3**. Values in all groups assessed pre-intervention were within published ranges (Jung et al., 2014; A. H. Young et al., 1999).

Table 2-3. UFC levels (mean, SDs) before and after 20x 20mg hydrocortisone / placebo

UFC (nmol/L)		Placebo	Hydrocortisone
Baseline	Male	41.00 (20.87)	38.13 (21.20)
	Female	48.60 (14.52)	28.89 (19.10)
	Total	**45.22 (17.50)**	**33.24 (20.04)**
Post-treatment	Male	41.75 (26.60)	360.88 (271.48)
	Female	52.70 (26.85)	559.11 (315.62)
	Total	**47.83 (26.54)**	**465.82 (304.06)**

There was a significant interaction effect between group and day of testing on UFC levels (group x day: $F(1,31)=40.39$, $p<0.001$; main effect of day: $F(1,31)=31.32$, $p<0.001$; main effect of group: $F(1,31)=29.42$, $p<0.001$)). Effects of gender were not significant (all $p>0.1$). The group x day interaction effect was driven by significantly higher UFC levels in the hydrocortisone group following treatment compared to the placebo group ($F(1,31)=34.60$, $p<0.001$). Additionally, there was a trend towards the placebo group showing higher cortisol levels pre-treatment (day 0) compared with the hydrocortisone group, however, this did not reach statistical significance (main effect of group: $F(1,32)=3.72$, $p=0.063$). Follow-up paired t-tests revealed a significant increase in absolute UFC levels from pre- to post-treatment in the hydrocortisone but not in the placebo group ($t(16)=-6.12$, $p<0.001$ and $t(17)=-0.34$, $p>0.7$, respectively). Time of waking was not significantly different between groups, testing days, or gender (all $p>0.1$).

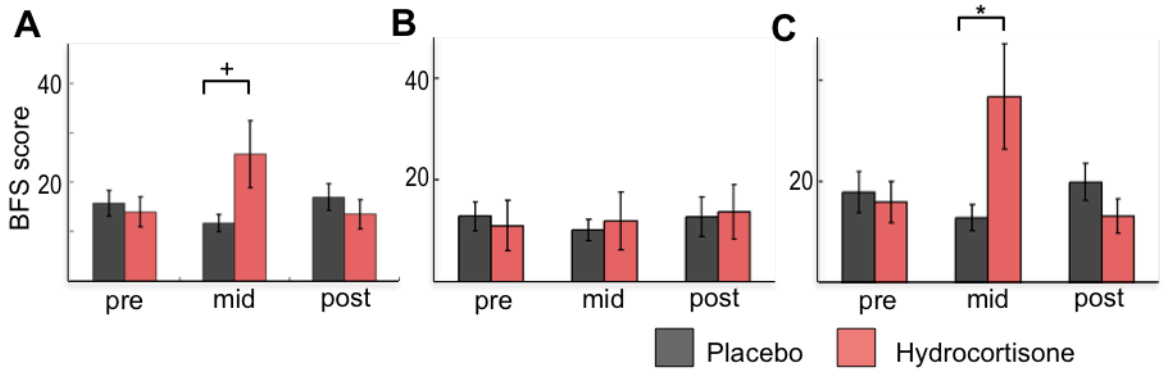
2.3.3. Self-report questionnaires

There was a significant interaction between testing day (day 1 vs. day 11), group, and sex on the STAI-State ($F(1,27)=4.58$, $p=0.042$), and a trend towards higher STAI-State scores post-testing

(mean=32.19, SD=7.80) compared with baseline (mean=30.58, SD=7.40; main effect of day: F(1,27)=3.46, p=0.074). The main effects of group and gender, and the remaining interactions were non-significant (all p>0.2). Separate follow-up ANOVAs for male and female participants revealed an interaction between day and group for male (F(1, 10)=6.28, p=0.031), but not for female participants (F(1,17)=0.44, p>0.5), with all other effects non-significant (all p>0.2). Males in the hydrocortisone (t(5)=-2.62, p=0.047), but not in the placebo group (placebo group: t(5)=1, p>0.3), reported increased STAI-S scores post-treatment compared to baseline. There were no significant effects of testing day, group, or gender on the PSS (all p>0.2) or BDI (all p>0.2).

Ratings of well-being as assessed with the BFS revealed a significant interaction effect between testing day (days 1, 6, and 11) and group (F(1.59, 42.81)=5.98, p=0.009). Follow-up t-tests for each testing day separately revealed higher BFS ratings (reflective of worse well-being) in the cortisol group compared to the placebo group at the study mid-point (day 6: t(19.16)=-1.99, p=0.06), with no group differences on at baseline (day 1: t(31)=0.42, p>0.6) or end of the treatment phase (day 11: t(32)=0.84, p>0.4; see **Figure 2-3**). The interaction effect between testing day and sex (F(2,42.81)=3.02, p=0.07), and between testing day and sex and group (F(1.59, 42.81)=3.29, p=0.06) were at trend. All other main and interaction effects were non-significant (all p>0.1).

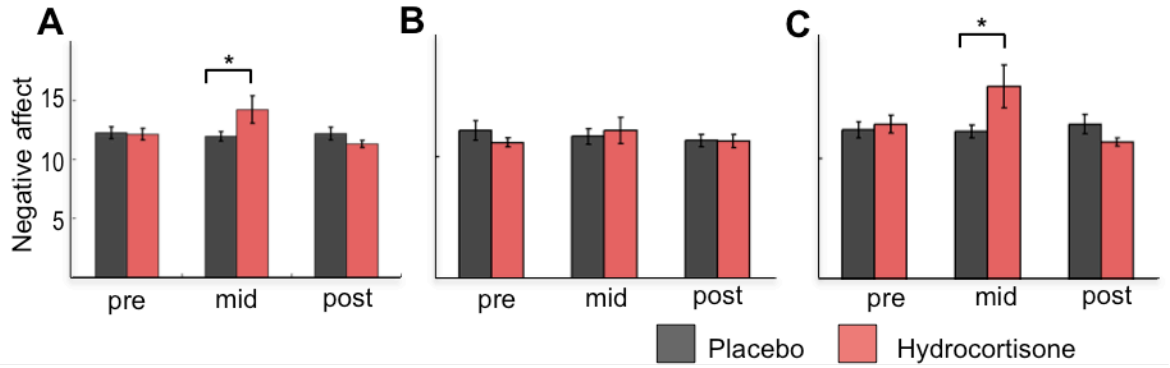
Figure 2-3. Scores on the Befindlichkeits-scale at the start, mid-point, and end of the study. A) All subjects, B) male, and C) female participants. BFS scores were higher in the hydrocortisone group compared with placebo at the mid-point of the study (driven by females), but not at the start or end of the hydrocortisone/placebo administration. Higher scores represent worse well-being.



Similarly, ratings on the PANAS-negative scale revealed significant effects of testing day (days 1, 6, and 11; F(1.84,49.58)=4.56, p=0.018), testing day by group interaction (F(1.84, 49.58)=4.90,

p=0.013), and testing day by group by gender interaction (F(1.84, 49.58)=3.45, p=0.043; see **Figure 2-4**). The effect of group (F(1,27)=0.39, p>0.5), and all remaining main and interaction effects were non-significant (all p>0.2). Separate ANOVAs for male and female participants revealed no significant effects in males (all p>0.1). In females, there was a significant interaction effect of day by group (F(1.47,23.55)=6.43, p=0.01), and a significant effect of testing day (F(1.47, 23.55)=4.77, p=0.027), while the main effect of group was non-significant (F(1,16)=0.81, p>0.3). Independent t-tests on females' scores revealed a trend for the hydrocortisone group to score higher than the placebo group at study mid-point (t(10.63)=-2.01, p=0.07), with no group differences at baseline (t(17)=-0.44, p>0.6) or end of treatment (t(17)=1.58, p>0.1). Paired t-tests within each group revealed a significant increase from day 1 to day 6 (t(16)=-2.48, p=0.025), and a significant decrease from day 6 to day 11 (t(16)=2.62, p=0.019) in the hydrocortisone group only. There were no differences between days for the placebo group (1-6: t(15)=0.81, p>0.4; 6-11: (t(16)=-.33, p>0.7), and no significant differences in either group between days 1 and 11 (placebo: t(14)=0.71, p>0.4); hydrocortisone: (t(15)=1.19, p>0.2).

Figure 2-4. Negative affect scores at the start, midpoint, and end of the study. A) All subjects, B) male, and C) female participants. PANAS-negative scores were higher in the hydrocortisone group compared with placebo at the mid-point (driven by females), but not at the start or end of the hydrocortisone/placebo administration



For the PANAS-positive scale, there was a significant testing day by group by gender interaction effect (F(2,54)=3.62, p=0.033). The main effect of testing day was at trend (F(2,54)=2.81, p=0.069), and all other main and interaction effects were non-significant (all ps>0.2). Follow-up ANOVAs in males and females separately revealed a significant decrease in positive affect from

mid- to end-point in all male participants (main effect of time: $F(2,22)=5.73$, $p=0.01$, pairwise comparison for day 6 vs. day 11 ($p=0.03$), day 1 vs. day 11 ($p=0.08$), day 1 vs. day 6 ($p=0.85$)), and in females receiving placebo (time x group interaction: $F(2,32)=3.53$, $p=0.04$; day 6 vs. day 11 ($p=0.006$); all other $p>0.1$), but not in females receiving hydrocortisone. Independent t-tests revealed no significant differences between females in the placebo and hydrocortisone groups (all $p>0.1$).

2.3.4. Side effects

There were minimal side effects reported by participants in either the placebo or hydrocortisone group, which were therefore not tested statistically. However, one female participant reported significant effects of restlessness and agitation after 3 days of treatment, and was discontinued from study participation in consultation with a medical professional.

2.4. Discussion

Repeated cortisol intake was associated with subjectively poorer wellbeing on a subset of measures. Specifically, the group receiving hydrocortisone rated their affect as subjectively worse than the placebo group at the mid-point (though not at baseline or at the end) of the study phase, an effect that was significant across the whole group but clearly driven by females, who showed a large increase in negative affect (PANAS-negative) and poorer well-being (BFS). Male participants in the hydrocortisone group, on the other hand, reported slight increases in state anxiety at the end of the treatment phase. Interaction effects revealed that all participants except the females receiving hydrocortisone rated their positive affect as lower towards the end of the study. Gender-specific increases in negative affect & state anxiety

2.4.1. Time- and gender-dependent effects

Our findings of increased negative affect in females at the mid-way point, and mildly increased state anxiety in males, suggest that further studies examining the effects of glucocorticoids on more sensitive and specific measures of subjective well-being are warranted. Importantly, we found that

subclinical psychiatric symptoms of depression, and subjective reports of stress were low across all participants and did not differ between treatment groups. The increased negative affect in female, but not male, participants, is in line with females reporting higher depressive psychopathologies (Kessler, 2003). Although not directly comparable given the difference in self-report measures, a previous study found that male participants receiving a closely similar regime of cortisol reported no adverse or psychiatric symptoms (A. H. Young et al., 1999). This further supports different susceptibility to glucocorticoid processes at the neural level in males and females, which may be a contributing factor to altered rates of prevalence (see e.g. Bangasser & Kawasumi, 2015).

Reports of clinically significant findings have most often emerged after chronic use of glucocorticoids (over several months to years), at which stage symptoms of depression and psychosis are most common (Brown, 2009; Brown et al., 2007; Ciriaco et al., 2013). Side effects of glucocorticoids at shorter durations have been reported to be qualitatively different, and more often include symptoms of hypomania or mania (as well as psychosis), although there are individual reports of increased depression appearing as early as the first weeks of treatment (Brown, 2009; Brown & Chandler, 2001). Nevertheless, a number of reports fail to show reliable effects of short-term (3-5 day) glucocorticoid medication on mood (Brown, Beard, Frol, & Rush, 2006; Wolkowitz et al., 1990, 2009), in line with the previous studies of repeated cortisol administration in healthy volunteers (McAllister-Williams. & Rugg, 2002; Sudheimer et al., 2012; A. H. Young et al., 1999).

Disparities in the reports of symptoms may in part be due differences in methodologies, with a number of studies using clinical scales to assess symptoms. Our study shows that subclinical scales of symptoms may be more sensitive to pharmacologically induced short-term changes in mood and well-being in healthy volunteers. This has previously been suggested in a study, which found no effect of 3-day prednisone administration on mood symptomatology in young healthy volunteers (Brown et al., 2006). Clinical scales are furthermore difficult to interpret given a certain amount of overlap in symptoms, for example, poor concentration, agitation, and insomnia, which can be signs of either depression or mania (Gift et al., 1989).

Increased negative affect was only evident in the hydrocortisone group at the mid-point of the study, suggesting the healthy participants may have recruited adaptive strategies following initial mood changes after repeated glucocorticoid administration. Furthermore, reports of symptoms following long-term glucocorticoid medications differ depending on the time course of administration, and suggest that manic symptoms are often apparent within days of first starting treatment (Brown et al., 2002; Naber et al., 1996; Wada et al., 2001), and depression more closely associated with longer-term administration even at low doses (Bolanos et al., 2004; Fardet et al., 2014; Frol et al., 2013; Gift et al., 1989). Conversely, our study suggests that healthy females may be particularly susceptible to rapid negative effects on mood and general well-being, although we did not test for symptoms of mania directly. Wolkowitz et al. (Wolkowitz et al., 1990) reported that there was large heterogeneity in the symptoms elicited by repeated glucocorticoid administration (5 days of prednisone) in healthy volunteers, with most participants reporting some form of symptoms. Given previous findings of side effects qualitatively changing over time, a reversible increase in negative affect may thus be reflective of the changing nature of side effects (i.e. to a dimension not captured by our measures), or an adaptation by healthy participants. Our results also revealed that all participants except the females receiving hydrocortisone rated their positive affect as lower towards the end of the study. However, given the effect in the placebo group, this may have captured an effect of study participation, for example, the amount of effort required, while in females receiving hydrocortisone, this effect may have been masked by the subsiding of negative well-being.

2.4.2. Cortisol manipulation

A 10-day placebo-controlled hydrocortisone intervention study in male and female participants revealed stark increases in cortisol, and gender-dependent effects on self-reported mood and wellbeing. Importantly, since responses to HPA axis challenges and behavioural measures described in subsequent chapters vary across populations, we recruited a homogeneous sample of healthy participants without any significant medical history. The placebo and hydrocortisone groups were well-matched across age, verbal IQ, perceived stress levels, and trait measures of

anxiety and personality. However, the hydrocortisone group was found to score particularly low on levels of neuroticism, which appeared to be driven by low scores for male participants receiving hydrocortisone. Nonetheless, the means of both groups fell into the low scorer range on the neuroticism scale suggesting that effects produced by this statistical difference are likely to be small. Cortisol administration caused stark increases in UFC levels in the hydrocortisone group, and these increases were reliably larger than individual variability across testing points in the placebo group, confirming that participants were compliant in taking the medication capsules. Nevertheless, our results confirmed reports of large heterogeneity in baseline levels of cortisol across individuals, and is in line with reports of highly variable endocrine responses to exogenous administration of glucocorticoids (see Judd et al., 2014; Wolkowitz et al., 2009).

2.4.3. Conclusions & Implications

Within the current study, altered negative affect was not tested for its relation to behavioural and neural effects of cortisol in the subsequent chapters due to the relatively small sample size. However, such links require further investigation due to their relevance in elucidating the complex interactions between subjective affect, cortisol levels, and behavioural performance (Abercrombie, Speck, & Monticelli, 2006; Ellenbogen et al., 2002). Similarly, some variability in responding may be mediated by measurable constructs such as trait negative affect (Abercrombie, Wirth, & Hoks, 2012; Portella, Harmer, Flint, Cowen, & Goodwin, 2005), and larger future studies may include these measures for their interpretational use.

Our findings of increased negative affect in females at the mid-way point, and mildly increased state anxiety in males, suggest that further studies examining the effects of glucocorticoids on more time-sensitive and specific measures of subjective well-being are warranted. Overall, however, our findings extend findings in animals, which – given the limited studies of repeated doses in humans – have so far provided the most controlled investigations of glucocorticoids directly and reliably altering clinically relevant phenotypes, both for depression-like behaviours (Sterner & Kalynchuk, 2010), and anxiety (Mitra & Sapolsky, 2008), following repeated corticosterone administration.

The following chapter investigates the effects of sustained cortisol increases on declarative and working memory, following on from previous reports of concomitant memory and mood alterations in healthy participants.

CHAPTER 3: EFFECTS OF REPEATED HYDROCORTISONE ADMINISTRATION ON MEMORY

3.1. Introduction

In the previous chapter, we found that repeated hydrocortisone administration was associated with a temporary increase in negative affect in healthy female at the midpoint of the study, and marginally increased state anxiety in healthy male participants. Given the extensive literature documenting effects of stressors on medial temporal lobe and prefrontal cortex physiology, and associated declarative memory and cognition, the current chapter aims to expand the scarce evidence on the impact of exogenous glucocorticoids on these modalities in humans. We therefore investigate the effects of the previously described 10-day course of hydrocortisone in a healthy sample on declarative and working memory tasks thought to be relevant to stress-related disorders.

3.1.1. Neutral & emotional declarative memory

As outlined in the General Introduction, the most pronounced structural and functional effects of repeated stress have been found in the hippocampus and surrounding regions of the medial temporal lobe. Alterations in declarative memory processing have been extensively studied in association with HPA axis abnormalities and stress-related psychiatric disorders (Dresler et al., 2011; Samuelson, 2011; Travis et al., 2016; Wingenfeld & Wolf, 2011; Wolf et al., 2016). Experimental manipulations of glucocorticoids during memory formation, retention, and recollection indicate that cortisol impacts different stages of hippocampal memory depending on the relative time and dosing of interventions (see Wolf et al., 2016). Human neuroimaging studies have linked increased hippocampal and parahippocampal activation during memory tasks with successful stimulus encoding and remembering (Alkire, Haier, Fallon, & Cahill, 1998; Bremner et

al., 2004; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Carr, Viskontas, Engel, & Knowlton, 2010). In a recent study, Sherwood Brown and colleagues (2015) found that repeated administration of hydrocortisone (160mg / day for 2.5 days) reduced hippocampal BOLD activation during viewing of familiar and novel pictures. Depressed patients have also been found to show reduced hippocampal activity during encoding of stimuli (Abercrombie et al., 2011; Bremner et al., 2004; Fairhall et al., 2010), further implicating altered hippocampal memory formation as a potential nexus for understanding abnormal glucocorticoid processes in the mechanisms and progression of functional deficits. On the other hand, stress appears to confer predominantly enhancing effects on memory for stimuli of emotional valence (Desmedt et al., 2015; Wolf, 2008). This improvement goes beyond the preferential processing of emotionally salient stimuli evident under baseline conditions (Buchanan & Lovallo, 2001; Hermans et al., 2014; Joëls et al., 2011; McGaugh, 2000), and is thought to be mediated by direct and indirect (via noradrenergic mechanisms) effects of cortisol on the amygdala (Adolphs et al., 1997), and its modulatory influences on the MTL and medial and orbitofrontal PFC (Hermans et al., 2014; L. Kilpatrick & Cahill, 2003). In order to assess both neutral and emotional memory, we employed well-validated declarative memory tasks that have shown relevance to cognitive and clinical impairments (Filippini et al., 2009, 2012; Harmer, O'Sullivan, et al., 2009; Harmer et al., 2004).

3.1.2. Working memory

Working memory – the ability to actively maintain information in the face of on-going information processing (Conway et al., 2005) – is thought to rely on neural substrates including regions of the prefrontal cortex such as the dorsolateral PFC (Arnsten & Jin, 2014; Aron, Robbins, & Poldrack, 2014; C. E. Curtis & D'Esposito, 2003), with concomitant decreases in the recruitment of hippocampal mechanisms (e.g. Symonds et al., 2012). Accordingly, its alterations by stress manipulations appear to be dissociable from declarative memory effects (Lupien, 1998; Lupien et al., 2007; Zobel et al., 2004). Although studies have found that cortisol has the ability to alter working memory (Lupien et al., 1999; Stauble et al., 2013; Symonds et al., 2012), results have not been fully consistent. Effects appear to depend on task properties, with some studies showing

cortisol effects on hippocampal versus PFC recruitment during working memory (Symonds et al., 2012), working memory in the context of emotional distraction (Oei et al., 2006, 2009), and strategy use (A. H. Young et al., 1999), indicating the field requires further study. Since effects of sustained cortisol increases on working memory have not been clearly delineated, we employed a well-validated task to assess working memory span following sustained increases in cortisol.

3.1.3. Chapter aims

Despite the large body of evidence from acute manipulations implicating cortisol in a variety of memory processes, effects of repeated, stress-level exposure to cortisol are still poorly understood. Based on evidence that cortisol exerts complex effects on memory in healthy participants depending on the processing domain and task properties, we predicted that a 10-day repeated hydrocortisone intervention in healthy volunteers (described in Chapter 2) would elicit dissociable effects on a selection of well-validated declarative and working memory tasks. Firstly, based on the above findings, we hypothesised neutral declarative memory performance to be impaired on a validated list learning task, and on an fMRI picture encoding task, with associated alterations in neural correlates in particular in the MTL and frontal cortex (Filippini et al., 2009). Furthermore, working memory as tested with the n-back task was also hypothesised to be impaired following glucocorticoid administration. Conversely, repeated cortisol was expected to enhance declarative emotional memory, with increases in performance specifically for negative items.

3.2. Materials & Methods

3.2.1. Participants & study design

The final sample consisted of 36 healthy participants (16 male). For a full overview of the study design and sample, please see Chapter 2.

3.2.2. Procedures and tasks

Participants completed a double-blind, placebo-controlled, between-subjects pharmacological intervention study. The current chapter addresses results from a picture encoding task completed while undergoing fMRI, and behavioural tasks of memory including an emotional categorisation, recall, and recognition paradigm, the n-back working memory task, the Rey Auditory Verbal Learning Task (AVLT), and a repeated measures assessment of digit span working memory, the latter all completed outside of the MRI scanner.

3.2.2.1. Encoding (functional MRI)

A whole-brain, single gradient echoplanar imaging (EPI) sequence was used to record BOLD activity during memory encoding of pictures (as described below). A single run of 50 T2-weighted slices was collected (TR = 3000ms, TE = 28ms, Flip angle = 90 degrees, FOV = 192mm, Voxel size = 3 x 3 x 3 mm, 180 measurements, Acquisition time = 9m 06sec).

The behavioural task was run using Presentation software (version 11.2, Neurobehavioral Systems). As described elsewhere (Filippini et al., 2009), the task stimuli consisted of 91 emotionally neutral colour pictures representing either landscapes or easily visible animals, which were approximately matched for complexity, brightness, and contrast. In a familiarisation task completed prior to entering the fMRI scanner, 8 pictures (4 animals, 4 landscapes) were displayed to the subjects 16 times in a pseudorandom order (image presentation = 3250 ms, ISI = 500 ms, between-block interval = 5000 ms). Participants were instructed to remember the images for later recognition and to respond according to whether the picture contained animals or not. To ensure satisfactory encoding, a recognition task was then performed (presenting 8 familiar and 8 unfamiliar images) which required participants to indicate whether the picture was familiar or new. Inside the MRI scanner (before commencing data collection), participants were shown the 8 familiar images twice in a pseudorandom order to allow familiarisation with the stimuli in the scanner environment. During the EPI sequence (detailed below), subjects were then presented with the 8 familiar images and 48 novel images (24 animals and 24 landscapes), displayed in a blocked

design (image presentation = 3250ms, interstimulus interval = 500ms, block duration = 30s). The subjects viewed 6 blocks each of 8 familiar and novel images, with rest blocks of 15 s between each block during which a fixation cross was shown. Participants were instructed to categorise images as containing animal or no animals (i.e. landscapes) by pressing response buttons, and to remember the images for a later memory task. About 45 minutes after the fMRI encoding, 83 images were presented on a computer screen outside the scanner for 4000 ms each (ISI = 1000 ms). These contained the 8 familiar images and 48 novel images presented during fMRI, and an additional 27 distractors (images not seen before; 13 animals and 14 landscapes), which were displayed in pseudorandom order. Participants selected from 2 responses according to whether they recognised the images as having been presented inside the scanner ('old') or not ('new').

3.2.2.2. Emotional categorisation & memory task

Participants completed a validated emotional memory task consisting of three parts.

Self-referential encoding: Sixty words representing either disagreeable (N=30) or agreeable (N=30) personality characteristics (from Anderson, 1968) and matched for word frequency, meaningfulness, and word length were presented in the centre of the screen for 500ms each. Participants were asked to categorise each word as quickly and accurately as possible according to whether they would like or dislike to be described by it, without being informed of the subsequent memory components of the task. Outcome measures for the emotional categorisation were classifications and reaction times.

Surprise recall: Subsequently, participants were instructed to recall and write down as many words as they could within a two-minute time limit. For the memory recall, the number of correct responses and false positives was recorded.

Recognition: Following the two-minute recall period, participants were presented with the 60 previously presented words (targets) and 60 novel words (matched distracters). Participants were asked to categorise these words according to whether they had been presented or not (familiar vs.

novel). Participants' memory recognition was assessed using correct responses, false positives, and reaction times.

3.2.2.3. N-back

Participants were asked to complete the n-back working memory task (see Owen, McMillan, Laird, & Bullmore, 2005), which consisted of monitoring sequentially presented (upper- and lower-case) letters and classifying the presented letter as the *same* as, or *different* to, the letter presented *n* trials previously in the sequence. Working memory load was manipulated by presenting blocks with different delays (i.e. number of trials, *n*) between the target letter and the cue, from *n* = 1-3. Additionally, a control condition was employed during which participants were asked to respond only when seeing the letter "X". A total of 16 blocks were presented, with each stimulus presented for 500ms, and brief rest periods between blocks. Participants' responses to keys marked "same" or "different" were recorded, and accuracy rates and reaction times analysed.

3.2.2.4. Rey Auditory Verbal Learning Test (AVLT)

Verbal learning and retention was measured using the Rey AVLT (see Vakil, Greenstein, & Blachstein, 2010), which required participants to learn (i.e. listen to and recall to the best of their ability) a list of 15 words (list A) presented by the researcher over five consecutive trials. The researcher then presented a new list of 15 words (list B) once, which the participant is asked to recall. Immediately following the list B recall, participants are asked to recall as many words as possible from list A. A surprise recall test was completed following a 15-20 minute delay (during which unrelated tasks were completed), at which point participants were asked to recall as many words as possible from list A. Finally, recognition memory was assessed by reading a list of words (including words from list A, list B, and novel words) and asking participants to classify them as presented in list A or not.

3.2.2.5. Digit span

The forward and backward digit span (see Schroeder, Twumasi-Ankrah, Baade, & Marshall, 2012; Wechsler, 1981) was administered as an additional measure of working memory before the start of

the study phase, and again on the final testing day. Participants were asked to listen to a sequence of digits, read out loud, and then repeat the sequence back in either forward or reverse order. Sequences were presented in ascending order of difficulty, from 3 to 8 digits (forward) and 2 to 7 digits (backward).

3.2.3. Analysis

3.2.3.1. fMRI encoding

fMRI data were analysed using the FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl; version 5.0.9; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009). Preprocessing, performed to improve statistical validity, was carried out using FEAT (FMRI Expert Analysis Tool; version 6.00), and consisted of MCFLIRT (FMRIB's Linear Image Registration Tool; Jenkinson, Bannister, Brady, & Smith, 2002) motion correction, deletion of non-brain tissue using BET (Brain Extraction Tool; Smith, 2002), spatial smoothing with a Gaussian kernel (5.00 mm full-width-half-maximum), grand-mean intensity normalisation of the entire 4D dataset by a single multiplication factor and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with a sigma of 70s), EPI distortion-correction using fieldmap images, and registration to a high-resolution image and to a standard MNI (Montreal Neurological Institute) template using FNIRT (FMRIB tool for small-displacement non-linear registration; Andersson, Jenkinson, Smith, & Andersson, 2007).

Subject-level fMRI analysis consisted of the computation of individual activation maps using a general linear model (GLM) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Task variables of interested consisted of contrasts between blocks of familiar pictures vs. fixation, novel pictures vs. fixation, and novel vs. familiar pictures (encoding). To increase statistical sensitivity, temporal derivatives were included as covariates. Variables were modelled by convolving the blocks of interest with a haemodynamic response function, using a variant of a gamma function (normalisation of the probability density function of the gamma function) with a standard deviation (SD) of 3 seconds and a mean lag of 6 seconds.

To compare activation in the hydrocortisone vs. placebo groups, whole-brain individual data were combined using FMRIB's Local Analysis of Mixed Effects (FLAME) across the whole brain, corrected for multiple comparisons (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The main contrasts of interest in the memory paradigm were novel vs. rest, familiar vs. rest, and novel vs. familiar (encoding). In addition to group (hydrocortisone vs. placebo) as the main factor of interest, the GLM included sex (male vs. female; deweighed mean), absolute and relative motion, and grey matter volume as regressors to correct for the influence of confounding factors. To reduce the influence of outlying data, outlier deweighing was used. Significant Z (Gaussianised T/F) statistic images were identified using cluster-based thresholding based on $Z>2.3$, and a family-wise-error (FWE) corrected cluster significance threshold of $p=0.05$ (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994).

ROI analysis

Based on a priori hypotheses that cortisol would influence memory processes in regions of the medial temporal lobe, we performed anatomical region of interest (ROI) analyses. Atlas-based masks for the hippocampus, and anterior and posterior parahippocampus (separately for each hemisphere) were created for each subject using the Harvard-Oxford brain atlas within FSL (thresholded at 50%). Individual ROIs were obtained using FMRIB's Integrated Registration and Segmentation Tool (FIRST; Patenaude, Smith, Kennedy, & Jenkinson, 2011), and visually inspected to ensure accuracy. Finally, ROIs were registered to functional coordinate space and FSL Featquery was used to extract BOLD percentage signal change in response to viewing of old (familiar) and new (novel) pictures. Signal change was analysed using a split-plot ANOVA with group (hydrocortisone vs. placebo) and gender (male vs. female) as between-subjects, and novelty (familiar vs. novel) and lateralisation (right vs. left hemisphere) as within-subjects factors.

Memory performance

A repeated-measures ANOVA with group and sex as between-subjects factor, and picture type (old, new, or distractor) as within-subjects factor was performed on the reaction times to old and

novel images during fMRI, and on the percentage of accurate responses and reaction times for correct responses in the post-scan recognition paradigm.

3.2.3.2. Behavioural tasks

Data from all trials were extracted in Matlab (version 8.2.0, R2013b), and trials containing responses above and below 3 SDs from an individual's mean were removed from the analyses in order to reduce the effects of outlying data. The behavioural outcome variables were then analysed in SPSS (version 22.0). Following log-transformation for non-normally distributed variables, data were analysed using mixed design ANOVAs, with treatment group (placebo vs. hydrocortisone) as the between-subjects factor and emotion and task condition as within-subjects factors. Sex (male vs. female) was included as a between-subjects factor in the analysis in order to control for gender effects, and Greenhouse-Geisser corrections were used when the assumption of sphericity was not met. Significant interactions were followed up using main effects analyses, with pairwise comparisons Sidak-adjusted to reduce the impact of multiple comparisons.

Emotional memory

No statistical testing was performed on emotional categorisation accuracies (endorsing positive items as liked and rating negative items as disliked) as group performance was at 100% for both the placebo and hydrocortisone groups. Repeated measures ANOVAs were performed on the percentage of words correctly recalled and recognised as familiar in the emotional surprise recall and recognition tasks, respectively, with valence as within-subjects factor and group and sex as between-subjects factor.

For the emotional categorisation and recognition tasks, reaction times below 200 ms and above 3000 ms and those above or below ± 3 SDs from individuals' means were removed as outlying data. Repeated measures ANOVAs were performed on reaction times (log-transformed when the assumption of normality was not met) with group and sex as between-subjects factors, and valence as within-subjects factor.

N-back

Due to a coding error in the computerised paradigm, datasets from 28 participants were available for analysis (13 placebo (5 males), 15 hydrocortisone (7 males)). Repeated-measures ANOVA were run on the percentage of correct hits in the 1-, 2-, and 3-back conditions, with difficulty as within-subjects factor and group and sex as between-subjects factors. Reaction times < 200ms and > 2000 ms, as well as those outside of ± 3 SDs from individuals' means were removed, log-transformed due to non-normality, and analysed using a repeated-measures ANOVA with difficulty (1-, 2-, or 3-back condition) as within-subjects factor, and group and sex as between-subjects factors.

Rey AVLT

Immediate recall (following initial learning of target and distractor lists), delayed recall (after 15-20 minutes), and recognition accuracy were analysed using between-groups ANOVAs with group and sex as factors (see Vakil et al., 2010).

3.3. Results

3.3.1. fMRI memory encoding

3.3.1.1. Behavioural results

During fMRI encoding, participants were faster to respond to familiar images compared to novel images when making animal/no animal responses ($F(1,29)=58.83$, $p<0.001$), but there was no significant effect of group ($F(1,29)=0.10$, $p=0.75$) or sex ($F(1,29)=1.63$, $p=0.21$), and all interaction effects were non-significant (all $p>0.1$).

The placebo and hydrocortisone groups did not differ on their post-scan recognition performance on either accuracy ($F(1,29)=0.75$, $p=0.40$) or reaction times ($F(1,29)=0.10$, $p=0.75$; see **Table 3-1**). Overall recognition performance was better for previously practised ('old) pictures compared to in-scan encoded ('novel') and distractor pictures, and better for distractor than 'novel' pictures (main effect of novelty: $F(2, 58)=108.89$, $p<0.001$; all paired comparisons significant at $p<0.05$). Reaction times during post-scan recognition followed the same pattern with fastest reaction times

to familiar images, and slowest reaction times to 'novel' pictures (main effect of novelty: $F(2,58)=72.09$, $p<0.001$). All other main and interaction effects were non-significant ($p>0.1$).

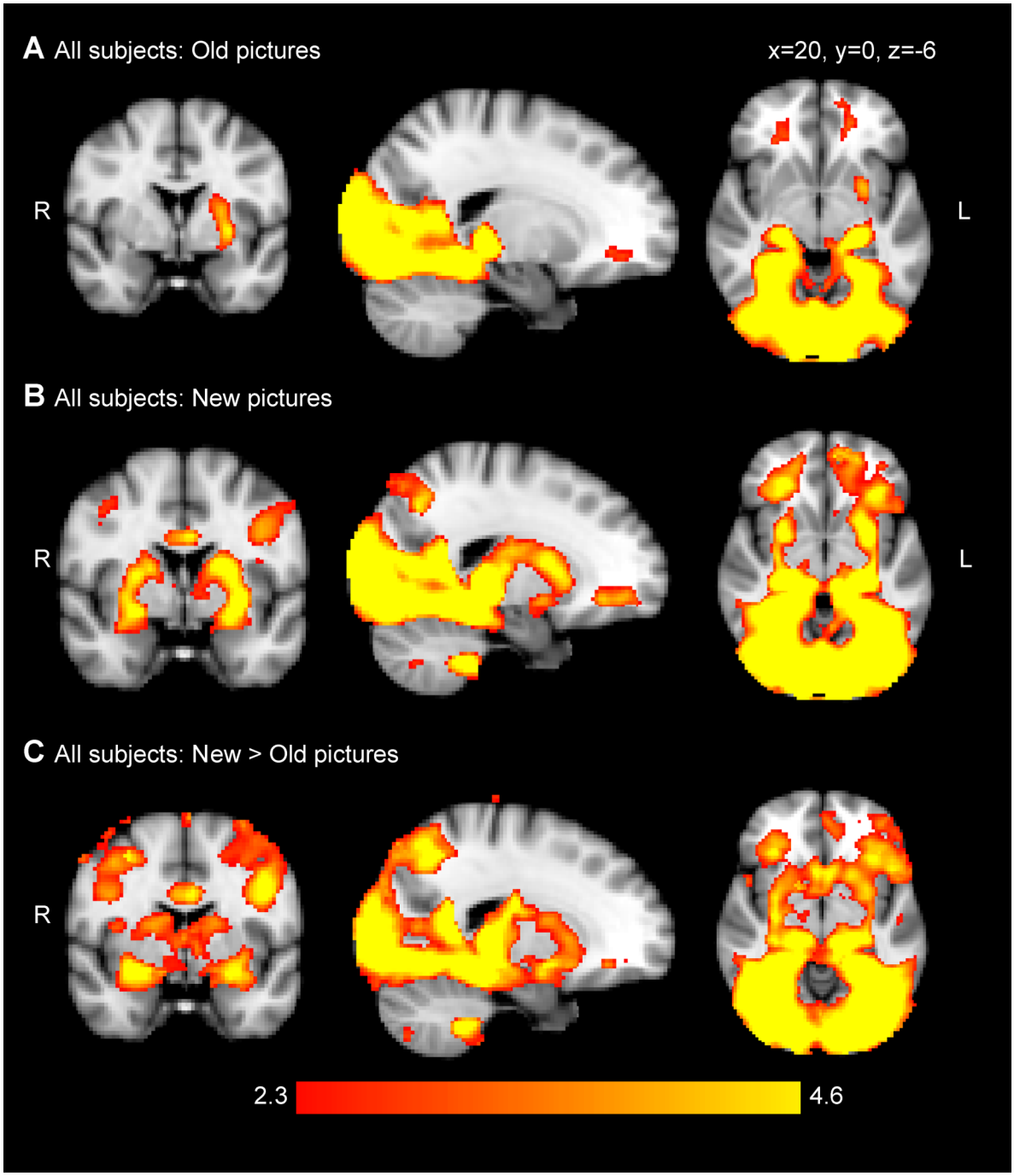
Table 3-1. Accuracy rates and reaction times (means ± SDs) on the neutral memory task.

		Placebo	Hydrocortisone
In-scan encoding			
Familiar	RT (ms)	660.52 (129.95)	683.43 (152.29)
Novel	RT (ms)	794.98 (192.70)	806.97 (184.76)
All	RT (ms)	727.81 (157.26)	745.27 (162.62)
Post-scan recognition			
Familiar	ACC (%)	97.66 (5.04)	97.06 (5.47)
	RT (ms)	839.37 (166.37)	885.36 (158.14)
Novel	ACC (%)	70.18 (12.95)	65.07 (15.19)
	RT (ms)	1205.72 (238.14)	1239.58 (235.28)
Distractor	ACC (%)	93.06 (5.56)	91.29 (8.78)
	RT (ms)	1157.14 (281.51)	1180.32 (264.60)
Overall	ACC (%)	80.27 (8.06)	76.68 (9.78)
	RT (ms)	1154.50 (237.84)	1186.06 (218.32)

3.3.1.2. All subjects

Brain areas previously associated with this picture encoding task (Filippini et al., 2009; Suri et al., 2014), including the medial temporal and occipital lobes, as well as the anterior cingulate cortex, and frontal areas were activated for the novel vs. familiar contrast (i.e. encoding new images compared to seeing previously learned images; see **Figure 3-1**).

Figure 3-1. Whole-brain activation during neutral picture viewing for all participants. Activation patterns (z-statistics thresholded at z=2.3) during viewing of (A) previously seen and (B) novel landscape / animal pictures. (C) Activation patterns for new vs. old pictures.

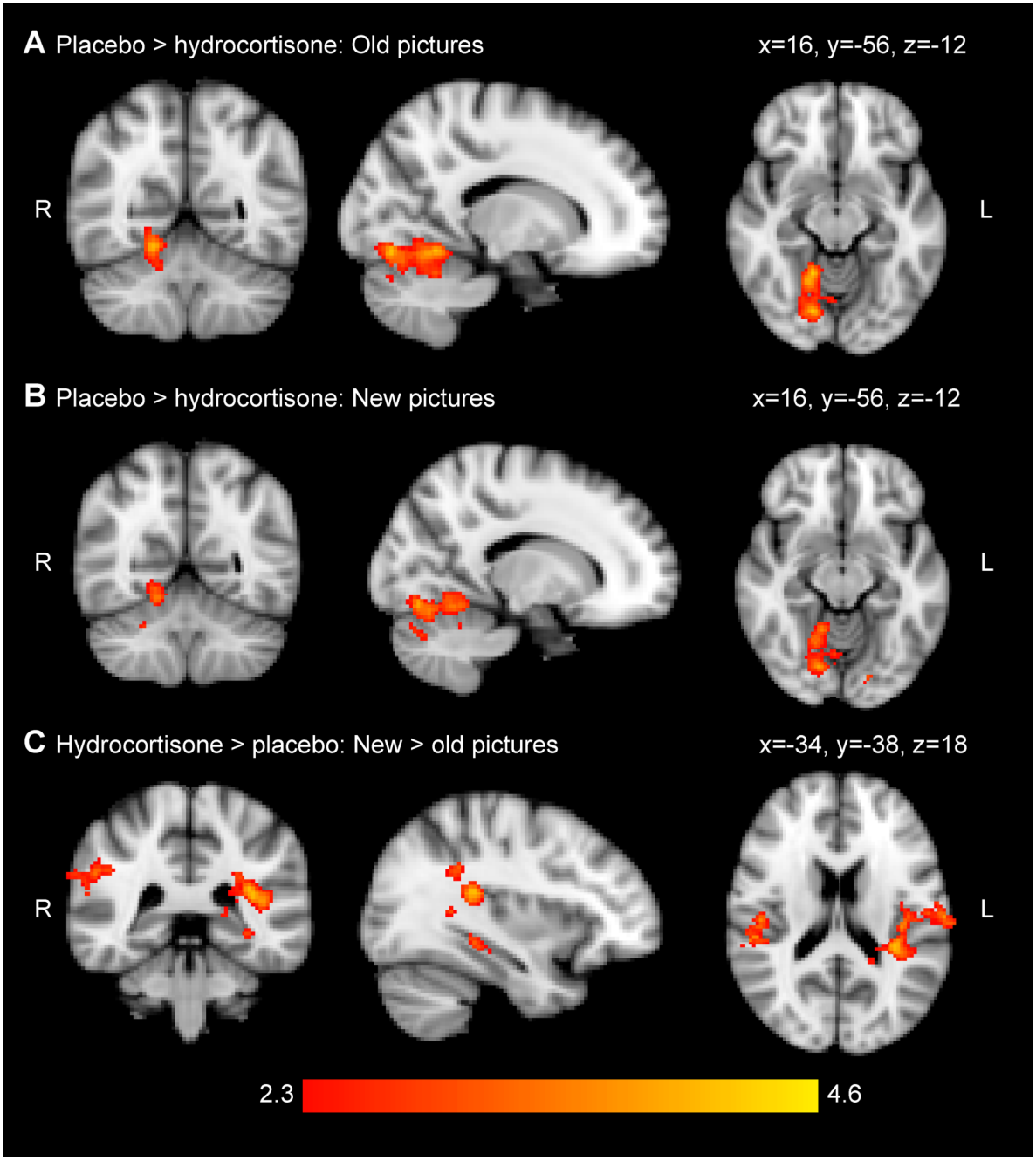


3.3.1.3. Hydrocortisone vs. placebo: Whole-brain analysis

Contrasting BOLD signal between the hydrocortisone and placebo group revealed reduced activation following hydrocortisone during both old and new pictures in areas previously associated with visual processing and encoding, most pronouncedly in the lingual and fusiform gyri. For the encoding contrast (new > old pictures), hydrocortisone showed higher activity in temporal and parietal regions, including the postcentral gyrus, inferior parietal gyrus, planum temporale, and regions previously associated with somatosensory processing (See **Table 3-2** and **Figure 3-2**).

Table 3-2. Brain areas differentially activated for placebo and hydrocortisone groups during the neutral memory paradigm.

Contrast	Cluster	# voxels	Brain regions	Z-max	Peak (x, y, z)
Placebo > Hydrocortisone					
Old	C2	1'436	Lingual gyrus, fusiform gyrus, cerebellum	4.15	16, -52, -12
	C1	482	Occipital pole, precuneus	4.27	4, -88, 30
Novel	C1	1'253	Occipital fusiform gyrus, cerebellum	4.30	-12, -80, -24
Hydrocortisone > Placebo					
Novel > Familiar	C2	933	Angular gyrus, parietal lobe (R)	3.84	64, -48, 34
	C1	1079	Planum temporale, parietal lobe (L) Postcentral gyrus, Hippocampus (L)	4.01	-34, -36, 18



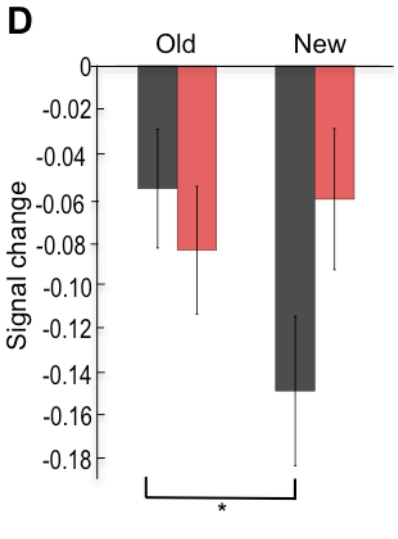
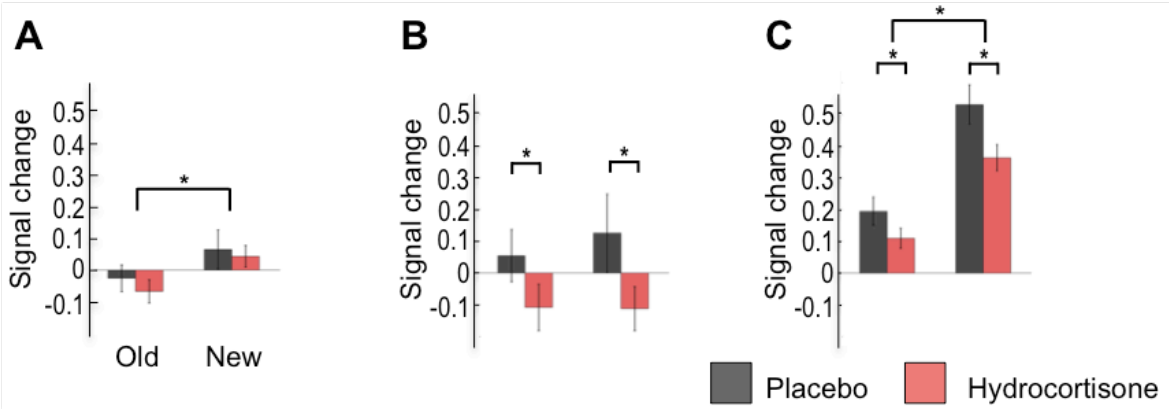


Figure 3-2. Activation differences between the placebo and cortisol groups during neutral picture viewing. Activation differences (z-statistics thresholded at z=2.3) during viewing of (A) previously seen and (B) novel landscape / animal pictures in the placebo > cortisol group. C) Hydrocortisone > placebo activation for viewing new versus old (encoding) pictures, and D) mean signal extraction from cluster activations. *p<0.05

3.3.1.4. ROI analysis

ROI analyses revealed higher hippocampal BOLD signal for novel compared to familiar pictures (main effect of novelty: $F(1,32)=11.29$, $p=0.002$), although this effect was not different between the groups ($F(1,32)=0.99$, $p=0.33$; see **Figure 3-3**). Higher activation for new > old pictures was also found in the posterior parahippocampus ($F(1,32)=137.89$, $p<0.001$)), but not in the anterior parahippocampus ($F(1,32)=1.14$, $p=0.29$). Furthermore, the hydrocortisone group showed lower activation for both old and new pictures compared to the placebo group in both the anterior and posterior parahippocampus (main effect of group: anterior ($F(1,32)=5.48$, $p=0.026$), posterior ($F(1,32)=5.91$, $p=0.021$)). Activation was higher in the right hemisphere compared to the left in the posterior parahippocampus (main effect of lateralisation ($F(1,32)=13.88$, $p=0.001$), and there was a significant lateralisation by novelty interaction effect in the posterior parahippocampus only ($F(1,32)=7.69$, $p=0.009$). All other main and interaction effects were non-significant (all p's>0.1).

Figure 3-3. Average percentage signal change in regions of interest. Mean (±SEM) percentage signal change averaged across right / left hemispheres of the A) hippocampus, B) anterior parahippocampus, and C) posterior parahippocampus. Masks based on Harvard-Oxford anatomical atlas. *p<0.05



3.3.2. Emotional categorisation & memory task

3.3.2.1. Emotional categorisation

Participants responded faster to positive (mean ± SD = 934.66 ms ± 170.96) compared to negative (mean ± SD = 1007.77 ms ± 199.23) self-referential personality words in the emotional categorisation task (valence x group ANOVA, main effect of valence: $F(1,32)=26.28$, $p<0.001$),

but the effect of group was non-significant (F(1,32)=0.01, p=0.93; see **Figure 3-4**). The main effect of sex (F(1,32)=0.56, p=0.46), group by sex interaction effect (F(1,32)=0.23, p=0.64), and group by valence interaction effect were non- significant (F(1,32)=1.61, p=0.21). The valence by gender interaction was at trend (F(1.32)=3.69, p=0.06)., and the valence by group by sex interaction effect was non-significant (F(1,32)=1.92, p>0.1).

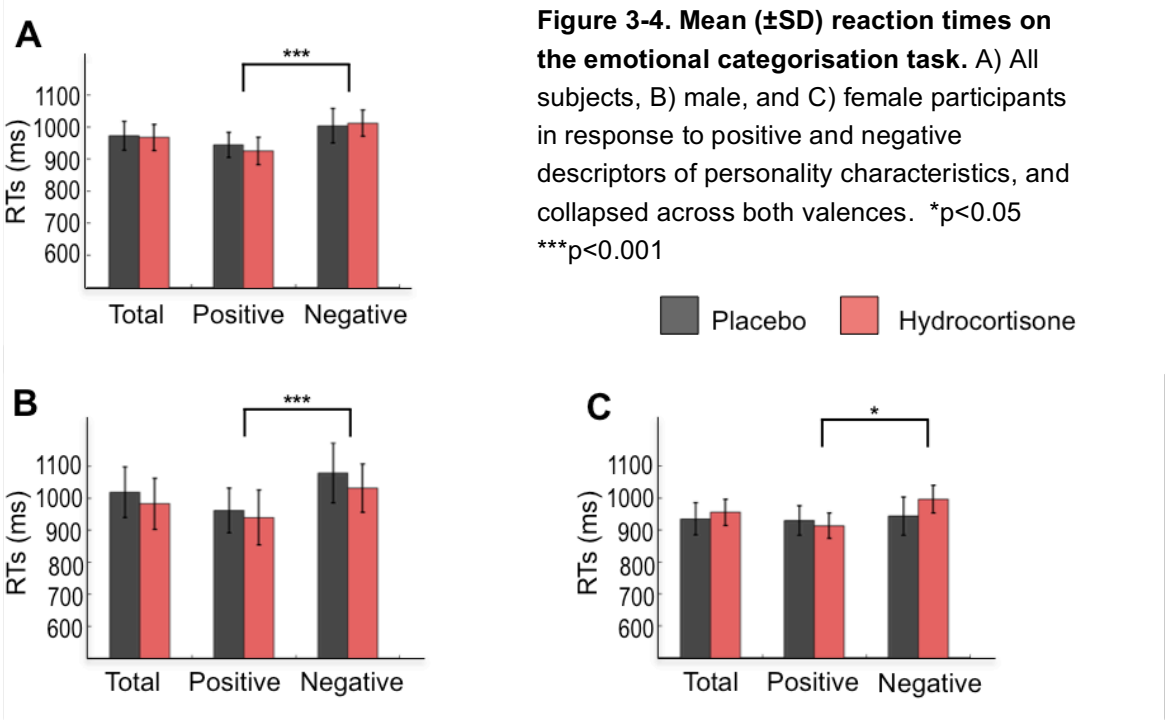


Figure 3-4. Mean (±SD) reaction times on the emotional categorisation task. A) All subjects, B) male, and C) female participants in response to positive and negative descriptors of personality characteristics, and collapsed across both valences. *p<0.05 ***p<0.001

3.3.2.2. Emotional surprise recall

A repeated measures ANOVA on absolute number of words recalled revealed a main effect of valence (mean ± SD positive words recalled = 6.94 (2.11), mean ± SD negative words recalled = 5.53 (2.05); (F(1,32)=7.40, p=0.01). The main effects of group (F(1,32)=2.04, p=0.16) and sex (F(1,32)=1.25, p=0.27), and all interaction effects (all p's > 0.1) were non-significant (see **Figure 3-5**).

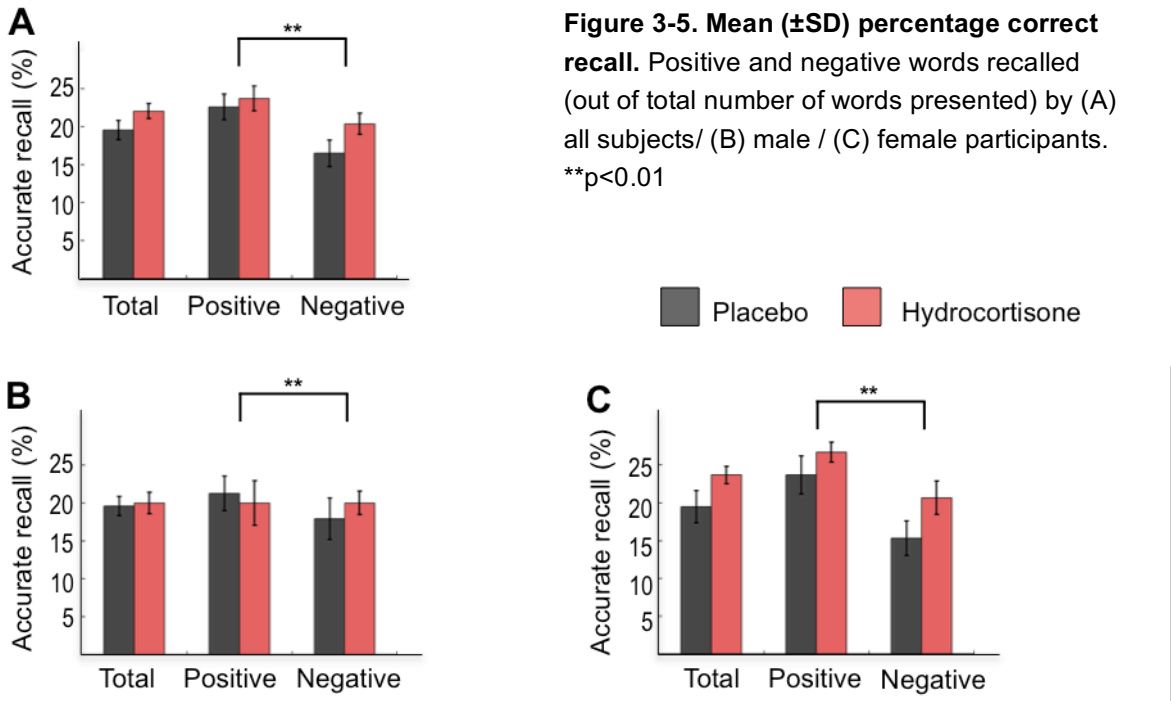


Figure 3-5. Mean (±SD) percentage correct recall. Positive and negative words recalled (out of total number of words presented) by (A) all subjects/ (B) male / (C) female participants. **p<0.01

3.3.2.3. Emotional recognition

Accuracies

The repeated measures ANOVA for percentage of correctly recognised words showed a significant effect of valence ($F(1,32)=18.62$, $p<0.001$), with participants recognising more positive (mean ± SD = 89.53 ± 8.00) than negative (mean ± SD = 81.48 ± 12.38) words (see **Figure 3-6**). There was also a significant effect of group ($F(1,32)=14.75$, $p=0.001$) with the hydrocortisone group (mean ± SD = 90.26 ± 5.34) recognising more words correctly than the placebo group (mean ± SD = 80.80 ± 9.31). There was no significant effect of sex ($F(1,32)=1.68$, $p=0.20$), and there were no significant interactions effects (all $p> 0.3$). The number of false positives (novel words classified as familiar) was not different between the groups ($F(1,32)=0.37$, $p=0.55$).

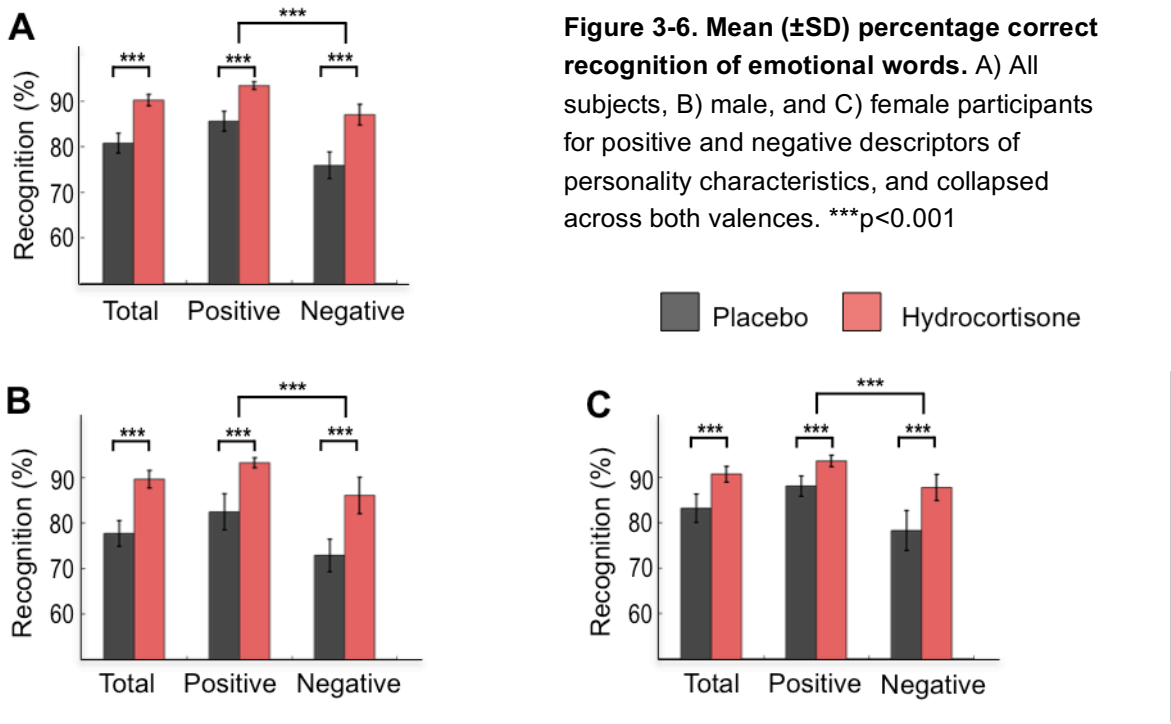


Figure 3-6. Mean (±SD) percentage correct recognition of emotional words. A) All subjects, B) male, and C) female participants for positive and negative descriptors of personality characteristics, and collapsed across both valences. ***p<0.001

Reaction times

A repeated measures ANOVA on log-transformed reaction times to correctly recognised words revealed a significant main effect of valence ($F(1,32)=25.19$, $p<0.001$), with participants recognising positively valenced words (mean ± SD = 1094.80 ms ± 203.88) more quickly than negatively valenced words (mean ± SD = 1174.29 ms ± 216.74; see **Figure 3-7**). The main effects of group ($F(1,32)=1.11$, $p=0.30$), sex ($F(1,32)=0.83$, $p=0.37$) and group*sex interaction ($F(1,32)=1.84$, $p=0.18$) were non-significant. The interaction effect of valence by group was at trend ($F(1,32)=3.10$, $p=0.09$), and all other interaction effects were non-significant (p's > 0.2).

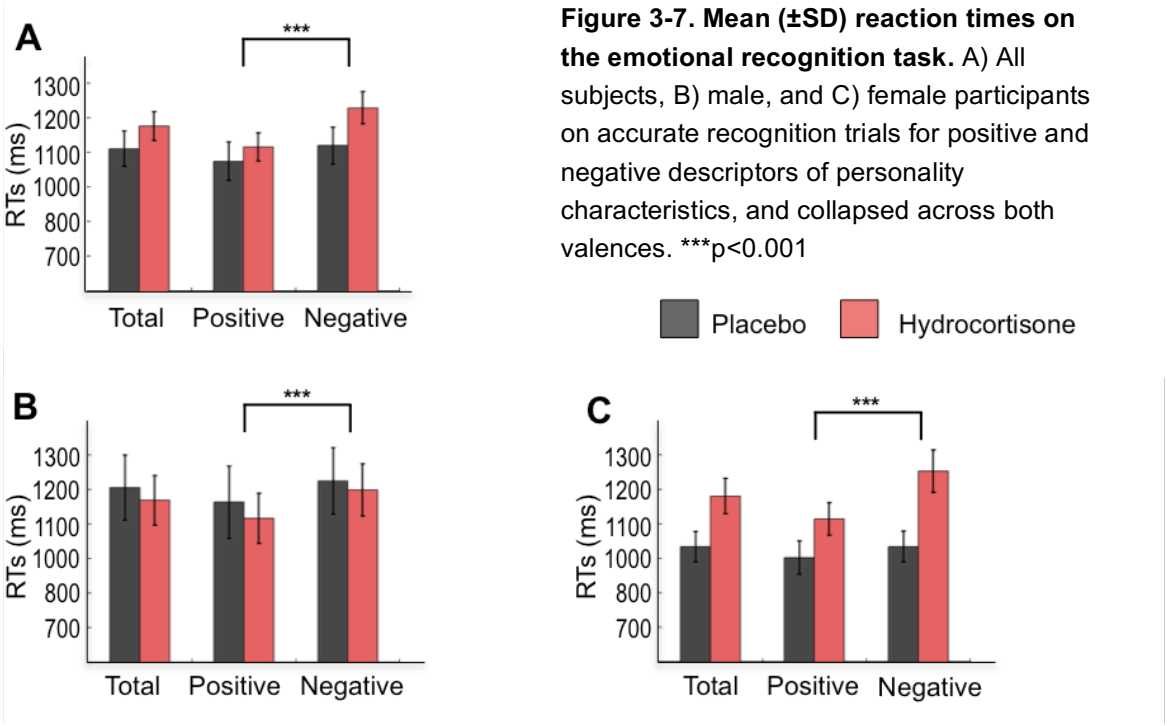


Figure 3-7. Mean (±SD) reaction times on the emotional recognition task. A) All subjects, B) male, and C) female participants on accurate recognition trials for positive and negative descriptors of personality characteristics, and collapsed across both valences. ***p<0.001

3.3.3. N-back working memory

There were no significant effects of group ($F(1,24)=0.01$, $p=0.95$) or sex ($F(1,24)=0.98$, $p=0.33$) on performance accuracy (percentage correct 'hits'). Increased task difficulty impaired participants' performance as shown by a significant main effect of difficulty ($F(2,48)=13.96$, $p<0.001$). All interaction effects were non-significant (all p's > 0.3; see **Table 3-3**)

Table 3-3. Mean (± SD) accuracy and reaction times on the n-back working memory task

Task	Measure	Placebo	Hydrocortisone
N-back (hit trials)			
Accuracy (%)	0-back (control)	92.31 (7.95)	87.77 (22.48)
	1-back	88.82 (11.08)	89.70 (12.89)
	2-back	74.13 (14.73)	73.91 (19.76)
	3-back	72.54 (12.01)	72.11 (19.76)
	Total	82.53 (5.59)	81.75 (14.39)
RT (ms)	0-back (control)	493.42 (58.86)	516.46 (107.64)
	1-back	541.56 (98.08)	591.52 (150.08)
	2-back	715.03 (255.70)	726.48 (221.82)
	3-back	698.90 (222.33)	728.53 (216.65)
	Total	597.47 (121.57)	628.17 (149.52)

Reaction times

The repeated measures ANOVA for log-transformed reaction times on correct hit trials in the 1-, 2- and 3-back conditions also revealed a significant main effect of difficulty ($F(2,48)=15.18$, $p<0.001$). There were no significant main effects of group ($F(1,24)=0.17$, $p=0.68$) or sex ($F(1,24)=2.23$, $p=0.15$) and all interaction effects were non-significant (all p's > 0.1).

3.3.4. Rey AVLT

Hydrocortisone and placebo treatment groups did not perform differently on total learning of words ($F(1,26)=0.08$, $p=0.78$), delayed recall ($F(1, 26)=1.80$, $p=0.19$), or recognition ($F(1,26)=0.77$, $p=0.39$; see **Table 3-4**). The main effects of sex were at trend for total learning ($F(1,26$, $p=0.05$) and recognition ($F(1,26)=3.82$, $p=0.06$), but not delayed recall ($F(1,26)=2.52$, $p=0.19$), with females' performance marginally better than males'. All other effects were non-significant ($p>0.1$).

Table 3-4. Mean (± SD) scores on the Rey Auditory Verbal Learning, and digit span tasks.

Task	Measure	Placebo	Hydrocortisone
AVLT			
Learning	Total (out of 75)	59.44 (6.15)	60.14 (5.93)
Recall	Delayed (out of 15)	12.44 (1.93)	13.21 (1.89)
Recognition	Total (out of 15)	14.38 (0.89)	14.64 (0.84)
Digit Span			
Baseline	Forward	8.56 (2.15)	9.50 (2.31)
	Backward	7.17 (1.89)	7.81 (2.74)
Testing day	Forward	9.62 (2.41)	10.19 (2.61)
	Backward	7.78 (1.93)	8.19 (3.33)

3.3.5. Digit span

Across all participants, performance was better on the forward compared to backward digit span showing the expected effect of difficulty ($F(1,30)=18.15$, $p<0.001$), and performance was improved on the second compared to first test day ($F(1,30)=5.20$, $p=0.03$; see **Table 3-4**). The main effects of group ($F(1,30)=1.03$, $p=0.32$) and sex ($F(1,30)=0.82$, $p=0.37$), and all interaction effects (all p's > 0.2) were non-significant.

3.4. Discussion

3.4.1. Overview

The aim of this chapter was to expand on previous findings of declarative and working memory alterations via glucocorticoid manipulations. Memory performance for neutral pictures was not significantly altered following cortisol administration, although ROI analyses revealed lower BOLD activity in the parahippocampus during viewing of neutral pictures for subsequent memory recognition. Additionally, participants receiving cortisol showed reduced BOLD activation in visual-occipital areas, and less deactivation during viewing of novel compared to familiar images (encoding) in somatosensory regions compared with the placebo group. Conversely, hydrocortisone improved emotional recognition memory of valenced self-relevant words. Behavioural performance on further declarative and working memory tasks was not significantly altered by hydrocortisone administration. These results largely support the modulatory role of cortisol on declarative memory, highlighting potentially opposing effects on memory for emotional materials and neutral hippocampal memory.

3.4.2. Reduced parahippocampal activation in absence of alterations in neutral memory performance

Overall, our results of reduced BOLD activation in anterior and posterior parahippocampal ROIs following repeated hydrocortisone support and extend wide-ranging evidence of cortisol's striking effects on the structure (e.g. Brown et al., 2015; Fuchs & Flügge, 1998; Sapolsky, 2000; Vyas, Mitra, Rao, & Chattarji, 2002) and function (e.g. Anacker et al., 2012; Caudal, Godsil, Mailliet, Bergerot, & Jay, 2010; Chaouloff & Groc, 2011; de Quervain et al., 2003; Maras & Baram, 2012) of the medial temporal lobe in both animals and humans. Previous studies have highlighted the parahippocampus as central to various stages of declarative memory processes (Bonner, Price, Peelle, & Grossman, 2015; de Quervain et al., 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Squire, Stark, & Clark, 2004; Wixted & Squire, 2011; Yonelinas, 2001), and our

findings of cortisol effects for both novel and familiar pictures were also non-specific for encoding of novel stimuli.

Interestingly, decreased activation following hydrocortisone administration was limited to the anterior and posterior parahippocampus, while the hippocampus proper showed altered activation to novel vs. familiar stimuli across both groups, which supports that hippocampal regions were activated for task-relevant processing and/or encoding of novel visual stimuli. The parahippocampal gyrus has previously been shown to be particularly sensitive to glucocorticoid modulation of memory, and higher concentrations of glucocorticoids may be required to induce more widespread hippocampal BOLD effects (e.g. Brown et al., 2013; de Quervain et al., 2003). A PET study administering a single (25mg) dose of cortisol found decreased blood flow in the parahippocampal gyrus (de Quervain et al., 2003), with less pronounced effects in other regions closely resembling our loci of group differences such as the MTL and visual cortex. Furthermore, a recent study found reductions in BOLD activation and after 2.5 days of (160mg/day) hydrocortisone in healthy participants (Brown et al., 2013), with the strongest cortisol-associated BOLD reductions in parahippocampal regions, but further reductions evident in the hippocampus.

In contrast to Brown and colleagues (2013), who found a trend towards impaired neutral declarative memory (on the Rey AVLT) following 2.5 days of a high (160mg/day) dose of hydrocortisone, we found no differences in performance on picture encoding or recognition performed before, during, and after fMRI scanning, or the Rey AVLT. Previous studies have linked higher parahippocampal activity with subsequent memory strength (Carr et al., 2010; de Quervain et al., 2003; Eldridge et al., 2000; O. Jackson & Schacter, 2004; Shrager, Kirwan, & Squire, 2008), particularly when involving partial recollection and contextual information processing (Barense, 2005; Graham, Barense, & Lee, 2010a), suggesting that decreased activation in the parahippocampus may be indicative of impaired MTL-dependent memory processes. Given our lack of behavioural group differences, we cannot conclusively dismiss alternative interpretations, such as equivalent levels of performance with reduced recruitment of hippocampal resources being indicative of increased memory efficiency (cf. Woodard et al., 1998). However, reduced

hippocampal activation has repeatedly been linked to declarative memory impairments when induced by cortisol increases, even when failing to show direct associations with hormone levels (de Quervain et al., 2003; Dorey et al., 2012; Lupien, 1998). It is thus more likely that the lack of behavioural effects in our study were a result of the relatively low doses of cortisol administered, an interpretation supported by a previous report of a 4-day course of 160mg/day, but not 40mg/day, of exogenous cortisol leading to poorer verbal declarative memory (Newcomer et al., 1999).

3.4.3. Altered activation in visual and sensory regions during neutral picture encoding

Unexpectedly, repeated hydrocortisone administration was also found to decrease activation during viewing of both novel and familiar neutral pictures in visual and somatosensory regions commonly activated during visual memory tasks (Cabeza & Nyberg, 2000). Participants who received hydrocortisone showed lower activation in the lingual and fusiform gyrus, structures previously found to underlie the encoding of visual memory (Kozlovskiy et al., 2014; Leshikar, Duarte, & Hertzog, 2012; Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000). Additionally, hydrocortisone attenuated a decrease in BOLD activation in auditory-somatosensory regions (including the superior temporal gyrus and parietal operculum) during encoding (i.e. viewing of novel versus familiar images) that was evident in participants receiving placebo. Given previous findings of the central role of the parahippocampus in the processing and encoding of high-level visual representations and its reception and projection back of information to sensory association areas (Barense, Gaffan, & Graham, 2007; Bonner et al., 2015; Graham, Barense, & Lee, 2010b), it is plausible that these alterations were related to the glucocorticoid-induced parahippocampal effects discussed above. For example, this decrease in sensory processing of pictorial task stimuli and decreased suppression of auditory areas may be indicative of reduced specificity for processing and encoding of non-affective task-relevant stimuli during the neutral memory task (i.e. novel pictures), and relatively increased processing of task-irrelevant but salient external stimuli (e.g. scanner noise) following increases in cortisol (see Schwabe, Joëls, et al., 2012; Schwabe & Wolf, 2013). Initial results of comparably reduced stimulus-driven BOLD activation associated with

sensory processing have been found in the superior temporal gyrus in patients with Cushing's syndrome (Langenecker et al., 2012), and in the cuneus in healthy volunteers when cortisol was administered several hours but not shortly prior to a fMRI during a verbal-emotional distraction task (Henckens, van Wingen, Joëls, & Fernández, 2012).

3.4.4. Increased emotional word recognition

Emotional word recognition (but not categorisation or free recall) was improved for positive and negative self-relevant personality adjectives in participants receiving hydrocortisone compared to placebo, in agreement with previous findings of a selectively enhancement of memory for emotional materials following cortisol administration (e.g. Buchanan & Lovallo, 2001). However, the valence non-specificity of the improvement for emotional words goes against research indicating that negative stimuli are more strongly altered in the context of psychiatric disorders (e.g. Hamilton & Gotlib, 2008; Toki et al., 2014). Given the healthy status of our sample, our findings of enhanced recognition memory for emotional words may be different to those seen in patients or at-risk populations. Furthermore, this effect may be indicative of non-glucocorticoid mechanisms involved in memory deficits in psychiatric symptoms and treatments, as supported by the ability of serotonergic antidepressants specifically modulating positive versus negative memory (Harmer et al., 2004), suggesting effects on valenced memory domains may be neurochemically specific. Risk status such as exposure to post-natal depression, thought to exert long-lasting effects on HPA axis functioning (Barry et al., 2015), has previously been linked to impairments in both positive and negative memory (Douglas & Harmer, 2011; Mannie et al., 2007), indicating that the negative biases in memory may be specific to patient populations and include additional mechanisms (Clewett, Schoeke, & Mather, 2014; Hamilton & Gotlib, 2008; Toki et al., 2014).

3.4.5. Declarative memory findings in context

Evidence suggests that arousal during encoding of valenced stimuli is at least partially responsible for improved memory for these items at later retrieval (Benno Roozendaal, 2003; Benno Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003). Emotional memory is thought to

be enhanced via both glucocorticoid and noradrenergic mechanisms (see Gagnon & Wagner, 2016; Hermans et al., 2014; Wolf, 2009; Wolf et al., 2016) and depends crucially on the amygdala exerting modulatory effects on brain regions including the hippocampus (de Voogd, Fernandez, & Hermans, 2016; Erickson, Drevets, & Schulkin, 2003; Hermans et al., 2014; Roozendaal, 2003; Roozendaal et al., 2003; Vaisvaser et al., 2013). Specifically, rapid catecholamine release in combination with non-genomic actions of cortisol has been proposed to enhance memory formation supported by amygdalar mechanisms, followed by genomic glucocorticoid facilitation of memory storage at the expense of processing unrelated stimuli (Lupien et al., 2007; Schönfeld, Ackermann, & Schwabe, 2014; Schwabe, Joëls, et al., 2012; Schwabe & Wolf, 2013; Schwabe, Wolf, & Oitzl, 2010).

Although speculative, such mechanisms may explain the disparate findings on the neutral and emotional memory tasks: in contrast to reduced recruitment of the medial temporal lobe under neutral conditions, the self-evaluative, emotional nature of the verbal encoding and surprise recall tasks may have led to the recruitment of amygdalar mechanisms that were enhanced by increases in cortisol levels (cf. Akirav & Richter-Levin, 2002, 2006). However, we were not able to rule out alternative factors in explaining these differences. In particular, we did not include tasks with both neutral and emotional stimuli in a directly comparable design, limiting this interpretation. Differences between the neutral picture and emotional word tasks, as well as the lack of direct matching of task difficulty may have played a role in the effects. However, we did include a neutral task with verbal stimuli (the Rey AVLT), which also showed no differences in behavioural performance between the hydrocortisone and placebo groups. The findings are thus in line with a qualitative distinction depending on the salience of stimuli, with the emotionally and personally salient memory task showing the strongest susceptibility to the effects of HPA-axis manipulations, and neural correlates of neutral memory suggesting a potential impairing effect of increased cortisol.

3.4.6. Working memory

We found no differences in working memory or general cognitive performance (as assessed with the n-back task and digit span) between the placebo and hydrocortisone group. Given previous findings of increased BOLD activity in the PFC and decreased activity in the hippocampus during the n-back task (Symonds et al., 2012), and that these brain areas are innervated by GR/MR (Bartsch, 2012; Herman et al., 2003; M. E. Jackson & Moghaddam, 2006), it is plausible that hydrocortisone administration impacted neural correlates of working memory in the absence of accompanying changes in behavioural performance, a dissociation that would be interesting to follow up in a future investigation. Furthermore, the absolute lack of effects of cortisol on these prefrontal-dependent processes in the present study, and the general inconsistencies in findings may reflect the complexity and specificity of cortisol on the PFC (which is differentially affected to MTL) and its behavioural correlates, given the wide-ranging functional domains and tasks of prefrontal function that have been tested (Lupien et al., 1999, 2007; A. H. Young et al., 1999). In support of this, there is evidence for an association between changes in cortisol levels and working memory when studied in patient populations (Zobel et al., 2004), and when the task contains an emotional component (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Grimm, Weigand, Kazzer, Jacobs, & Bajbouj, 2012; Oei et al., 2006, 2009). For example, Oei and colleagues (2009, 2011) in a sequence of studies have shown that hydrocortisone - administered acutely - can influence working memory performance when emotionally distracting materials are also presented, and that in this domain, impairments can be linked with psychiatric symptoms.

3.4.7. Conclusions & Implications

Repeated hydrocortisone administration improved recognition memory of emotional words in both male and female healthy volunteers, with no effects on neutral memory performance, although differences in neural correlates of neutral picture encoding suggest a modulatory and potentially impairing role of glucocorticoids on the medial temporal lobe. In our current sample of healthy young participants, sustained increases in cortisol manipulation showed no further effects on

working memory performance. Our findings are in support of tasks involving emotional stimuli showing increased sensitivity to the effects of glucocorticoids, and that effects of cortisol on working memory performance may overall be less pronounced than those on declarative memory. Given limited evidence of the impact of sustained cortisol on emotional processing in domains other than memory, the subsequent chapter investigates how cortisol increases associated with the 10-day hydrocortisone manipulation alters emotional attention and recognition.

CHAPTER 4: EFFECTS OF REPEATED HYDROCORTISONE ADMINISTRATION ON EMOTIONAL ATTENTION, PERCEPTION, AND RECOGNITION

4.1. Introduction

Chapters 2-3 demonstrated that repeated cortisol administration increased subjective ratings of anxiety and negative affect in healthy male and female volunteers, respectively. The same participants showed alterations during memory task performance interpreted as directionally opposite for emotional versus neutral memory, with increased recognition of valenced words, and decreased parahippocampal activity during neutral stimulus encoding following cortisol. The current chapter investigates the effects of repeated cortisol on the perception of, attentional to, and interpretation of emotionally salient information, predominantly facial expressions.

4.1.1. Emotional attention and perception

In addition to the previously discussed enhancements in memory for negative stimuli, prominent features of depressive disorders (and risk thereof) include the interpretation of materials as less positive and more negative (e.g. S. W. Y. Chan, Goodwin, & Harmer, 2007; Hsu, Langenecker, Kennedy, Zubieta, & Heitzeg, 2010; Lee et al., 2007). Individuals with depression have been found to identify ambiguous and neutral stimuli as more negative, to show larger biases towards negative versus positive stimuli, and to preferentially process negative information compared to healthy controls (for reviews, see Kemp & Felmingham, 2008; Kircanski & Gotlib, 2015; Kret & Ploeger, 2015). Stress-related disorders have furthermore been linked with attentional biases, with extensive evidence supporting a close link between biases in the rapid attentional processing of salient negative, particularly threat-related, stimuli and symptoms of anxiety, and evidence for attentional

biases particularly at longer stimulus durations in depression (for reviews, see Larson, Nitschke, & Davidson, 2007; Mogg & Bradley, 2005; Peckham et al., 2010).

4.1.2. Facial emotion perception & interpretation

Findings of altered perception and recognition of facial expressions most reliably relate depressive disorders with reduced processing of positive and increased processing of negative facial expressions, including specific enhancements for sadness (e.g. Fu et al., 2004; Keedwell et al., 2010; Sheline et al., 2001; Surguladze et al., 2004, 2005, 2010; Victor et al., 2010). Anxiety disorders and high subclinical levels of anxiety, on the other hand, have been associated with abnormal processing of and responding to fear- and threat-related social stimuli (e.g. Bradley et al., 1998; Etkin et al., 2004; Gentili et al., 2016; Mogg & Bradley, 2005; Pishyar, Harris, & Menzies, 2004; Staugaard, 2010; Tran, Lamplmayr, Pintzinger, & Pfabigan, 2013). Neurally, altered BOLD signal to facial expressions in psychiatric disorders converges on a network of regions including the hippocampus, thalamus, insula, anterior cingulate cortex, and areas of the medial PFC (for a review, see Bourke et al., 2010; see also Kober et al., 2008; Leppänen, 2006). In addition, consistent with its central role in the detection of affective significance, emotional face processing involves pronounced recruitment of the amygdala (Adolphs et al., 1999; Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Sergerie, Chochol, & Armony, 2008).

4.1.3. Non-acute glucocorticoid intervention studies

Overwhelming evidence points to the importance of emotional information processing biases for a more systematic understanding of the symptomatic time course of psychiatric treatment and disease (Harmer et al., 2011; Ritchey et al., 2011; Roiser et al., 2011; Warren, Pringle, & Harmer, 2015b), yet how these are modulated by sustained HPA-axis alterations has not been conclusively characterised (Cowen, 2009). Patients with endogenous hypercortisolaemia due to Cushing's disease show increased BOLD in frontal and subcortical and poorer ability to identify emotional facial expressions (Langenecker et al., 2012). Conversely, in a study closely resembling our design, 5-day repeated cortisol decreased neural activity evoked by sad, but not happy or fearful, faces in

healthy males (Sudheimer et al., 2012). This suggests sustained glucocorticoid fluctuations are relevant for the perception and interpretation specifically of negative face stimuli. Evidence, however, remains inconclusive regarding specificity of negative valences and associated behavioural performance and discrimination ability in different populations (Buades-Rotger, Serfling, Harbeck, Brabant, & Krämer, 2016; S. Li, Weerda, Milde, Wolf, & Thiel, 2014; Mather, Lighthall, Nga, & Gorlick, 2010; Putman, Hermans, & van Honk, 2007; Sudheimer et al., 2012).

4.1.4. Chapter aims

Despite the clinical relevance of persistent alterations in HPA axis functioning, few studies have investigated the direct impact of sustained increases in cortisol on emotional processing. The current chapter investigates the effects of repeated hydrocortisone on emotional attention, perception, and recognition, with a particular focus on facial emotion perception and recognition. This includes the results from a gender categorisation task of emotional facial expressions, completed while undergoing a fMRI scan and behavioural results from an emotion categorisation task of emotional facial expressions. Additionally, findings from an attentional dot-probe task and a continuous flash suppression task are presented.

4.2. Materials & Methods

4.2.1. Participants & study design

Participants completed these as part of the final study appointment of the hydrocortisone study. For a full overview of the study methodology and procedure, and the final sample of 36 healthy participants (16 males), please refer to Chapter 2.

4.2.2. Procedures and tasks

4.2.2.1. Facial Expression Perception Task (FEPT) – MRI gender categorisation

Functional neuroimaging data was acquired at 3 Tesla field strength using a single run of an echo-planar imaging (EPI) sequence covering the whole brain (TR = 3000 ms, TE = 30 ms, field of view

= 192 mm, flip angle = 87°, voxel dimension = 3.0 x 3.0 x 3.0 mm, acquisition time = 14 min 6 s). Participants were instructed to classify the gender of faces (male or female) with fearful, happy, or angry expressions by pressing a key on a MRI-compatible button box. For each trial, a fixation cross was presented for 2900 ms, followed by the emotional face for 100 ms. A total of 12 blocks of alternating valence were presented (4 blocks per valence), with 10 trials of the same valence per block. A fixation cross was presented for 30 seconds of rest between blocks. Stimuli were presented onto a screen at the back of the scanner bore (visible to the participant in angled mirrors) using E-Prime (version 2.0; Psychology Software Tools Inc., Pittsburgh, Pennsylvania).

4.2.2.2. Facial Expression Recognition Task – behavioural emotion recognition

Images of faces expressing one of six emotions – happiness, surprise, sadness, fear, anger, disgust (taken from the Pictures of Affect series; Ekman & Friesen, 1976) – were displayed at 10 morphed intensity levels from neutral to maximum emotional expression (as described in Harmer et al., 2004). Additionally, faces containing a neutral expression were shown, leading to a total of 250 randomly presented stimuli. Each stimulus was presented for 500 ms and replaced by a grey screen until the participant, instructed to categorise the emotion of the face as quickly and accurately as possible, responded by selecting a key corresponding to one of the emotions. The outcome measures were classification accuracy, number of misclassifications, and reaction times.

4.2.2.3. Attentional dot probe

60 negative and 60 positive words were paired with neutral words matched for length. On each trial, a fixation cross was presented for 500 ms in the centre of the screen, followed by two words presented at the top and bottom of the screen. In the unmasked condition, the words were presented for 500 ms. In the masked condition, word pairs were presented for 17 ms after which a mask was displayed for 483 ms. Masks were constructed from digits, letters, and non-letter symbols and were matched for word position and length. Words or masks were replaced by a probe of either one or two stars in the location of one of the preceding stimuli (probes were presented at the top or bottom of the screen with equal frequency). Participants were instructed to indicate the number of stars as quickly and accurately as possible using two labelled keys. A key press terminated the probe

presentation and trial. There were 180 trials in total (30 positive-neutral, 30 negative-neutral, 30 neutral-neutral word pairs each for masked and unmasked conditions), and emotional words were presented at the top and the bottom location with equal frequency. Masked and unmasked trials were presented in random order. Reaction time and accuracy scores were recorded, and attentional vigilance scores were calculated for each participant by subtracting the reaction time from trials when probes appeared in the same position as the emotional word (congruent trials) from those trials when probes appeared in the opposite position to the emotional word (incongruent trials).

4.2.2.4. Continuous Flash Suppression

The presentation parameters of the continuous flash suppression task have been described in full elsewhere (Capitao, 2014; Yang, Zald, & Blake, 2007). In brief, stimuli consisting of faces with neutral, happy, or fearful expressions (from Ekman & Friesen, 1976) were presented using a mirror stereoscope and black divider, aligned to create binocular fusion when participants viewed the stimuli on a LCD monitor. Each eye was presented with a black square on one half of the screen, with one square containing a suppressor mask consisting of a dynamic Mondrian pattern, and the other a face image positioned in one quadrant. In the initial 1000 ms, the Mondrian mask was presented at full contrast, whereas the face image had low contrast (20%) in order to achieve strong initial suppression of the face stimulus. Thereafter, the face image was gradually increased to full contrast, followed by a gradual decrease in the contrast of the Mondrian pattern. The face remained at full contrast until a response was made. Participants received 6 practice trials prior to the start of the experiment with neutral faces not otherwise used in the experiment. 180 trials were presented in total, with 60 trials each for neutral, happy, and fearful facial expressions. Participants were instructed to respond to the face location by pressing one of four marked keys on a computer keyboard as quickly and accurately as possible, as soon as they were able to locate the face (i.e. even when the face was only partially visible). Visual and auditory feedback was given for incorrect responses. Stimuli and locations were randomised across trials, and stimuli were presented using Matlab version 2010a (Mathworks, Inc., with Psychtoolbox-3 [http://psychtoolbox.org/]).

4.2.3. Analysis

4.2.3.1. FERT-MRI gender categorisation

fMRI scans from all 36 participants described in Chapter 2 were available, yielding datasets from 20 female and 16 male participants. The FSL preprocessing and first-level analyses were completed using the same settings as those described for the neutral picture-encoding task (Chapter 3), except for the task-specific design parameters. Briefly, preprocessing consisted of motion correction, brain extraction, spatial smoothing, intensity normalisation, registration, and field map correction. Following preprocessing, individual activation maps for contrasts between each emotion (fearful, happy, and angry faces) compared to fixation were computed by convolving the blocks of interest with the haemodynamic response function. To contrast activation in the hydrocortisone vs. placebo groups, whole-brain individual data were combined using mixed-effects group cluster analysis, corrected for multiple comparisons. Significant group differences in activation were identified using cluster-based thresholding of statistical images with confound regressors (absolute and relative motion, gender, grey matter volume) and outlier deweighing (z-threshold=2.3, corrected spatial extent threshold of p=0.05).

All button-press responses categorising happy, fearful, and angry faces as either male or female were analysed for accuracy and reaction times using repeated-measures ANOVA with between-subjects factors of group (placebo, hydrocortisone) and sex (male, female), and emotion (fearful, happy, and angry) as a within-subjects factor.

Atlas-based masks for ROI analyses in the hippocampus, amygdala, and thalamus were created using the same procedure as described in Chapter 3. Timecourse signals from each ROI were extracted for fearful, happy, and angry pictures using FSL Featquery and analysed using a split-plot ANOVA with group (hydrocortisone vs. placebo) and sex (male vs. female) as between-subjects, and emotion (fearful, happy, angry) and lateralisation (right vs. left hemisphere) as within-subjects factors.

4.2.3.2. Behavioural tasks

Data from all trials were extracted in Matlab (version 8.2.0, R2013b). For each task, trials containing responses above and below 3 SDs from an individual's mean were removed from analysis in order to reduce the effects of outlying data. Following log-transformation for non-normally distributed variables, the behavioural outcome variables were analysed in SPSS (version 22.0) using mixed design ANOVAs, with treatment group (placebo vs. hydrocortisone) and sex (male vs. female) as the between-subjects factors and emotion and task condition as within-subjects factors. Greenhouse-Geisser corrections were used when the assumption of sphericity was not met. Significant interaction effects were followed up using main effects analyses, with pairwise comparisons Sidak-adjusted to reduce the impact of multiple comparisons.

4.3. Results

4.3.1. FERT-MRI gender categorisation

4.3.1.1. Behavioural performance

Males performed significantly better than females on during the FERT-MRI (main effect of sex ($F(1,32)=4.61$, $p=0.04$; see **Table 4-1**), and there was a trend towards a significant interaction between sex and group ($F1,32)=3.58$, $p=0.068$). No significant effects of treatment group ($F(1,32)=0.05$, $p=0.83$) or valence ($F(1.57, 50.12)=0.47$, $p=0.63$) were observed on total gender categorisation accuracies. All other interaction effects were non-significant (all p-values > 0.6).

Table 4-1. Behavioural performance on the FEPT-MRI. Mean (± SD) accuracy rates and reaction times categorising facial stimuli as male or female. Overall, males participants showed higher accuracy rates than female participants.

		Placebo	CORT	Total
Accuracy (%)	Male	95.83 (1.94)	98.02 (1.72)	96.93* (2.10)
	Female	95.50 (2.84)	92.75 (6.37)	94.13* (5.00)
	Total	95.65 (2.42)	95.09 (5.48)	95.37 (4.18)
Reaction time (ms)	Male	662.50 (89.12)	688.78 (166.09)	675.64 (129.48)
	Female	636.28 (93.41)	670.27 (81.02)	653.27 (86.87)
	Total	647.93 (89.83)	678.49 (122.16)	663.21 (106.81)

There was a significant effect of valence on reaction times ($F(2,64)=5.64$, $p=0.006$), driven by faster reaction times for happy vs. fearful ($p=0.042$) and for happy vs. angry faces ($p=0.007$), with no significant difference between angry vs. fearful faces ($p=0.961$). The main effects of group ($F(1,32)=0.67$, $p=0.42$) and sex ($F(1,32)=0.37$, $p=0.55$) and all interaction effects were non-significant (all p's>0.1).

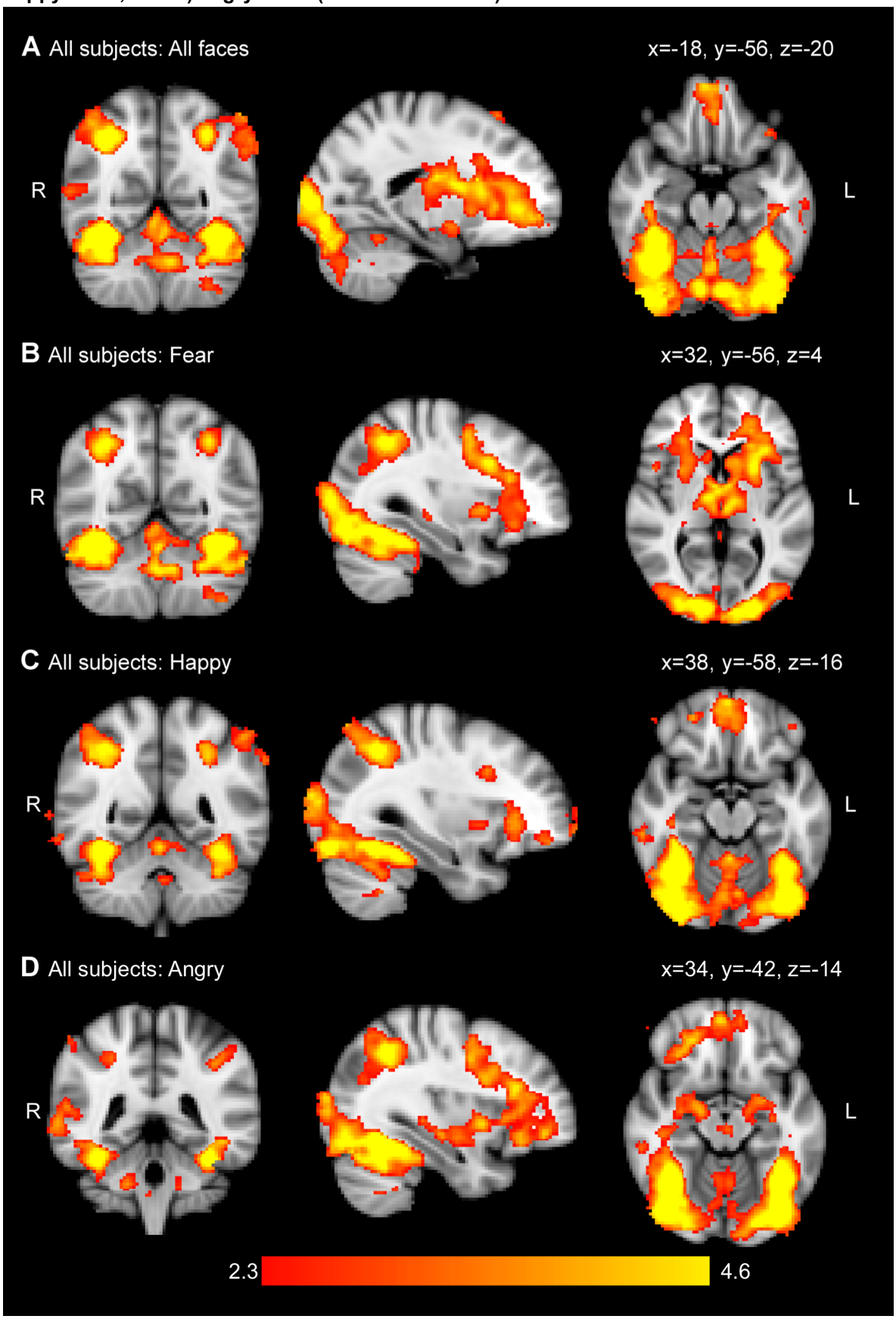
4.3.1.2. All subjects – task activation

Brief viewing of male and female faces activated a wide network of brain areas previously associated with viewing of emotional faces. Subregions of the occipito-visual, parietal, and medial prefrontal cortices showed areas of increased BOLD compared to fixation for all (fearful, happy, and angry) faces across all participants as depicted in **Table 4-2** and **Figure 4-1**.

Table 4-2. Overview of BOLD activation clusters across all subjects for main emotional faces versus fixation contrasts. L=Left hemisphere, R=Right hemisphere.

Emotion	Cluster	# of voxels	Brain regions	Max. Z	Peak (x, y, z)
Fear	C3	36'097	Occipital fusiform, temporal occipital, lingual gyrus, cerebellum (bilateral)	6.66	-32, -84, -14
	C2	1'244	Parietal (R) (superior parietal lobule / angular gyrus)	5.36	34, -54, 44
	C1	764	Parietal (L) (superior parietal lobule / angular gyrus)	2.41	-26, -48, 46
Happy	C7	14'177	Occipital fusiform, temporal occipital, lateral occipital, occipital pole	7.20	-40, -56, -18
	C6	7'146	Middle frontal gyrus (R), Precentral gyrus (R)	4.99	40, 26, 26
	C5	1'903	Angular gyrus, lateral occipital (superior) (R)	5.86	36, -56, 42
	C4	1'146	Angular gyrus, lateral occipital (superior) (L)	4.78	-30, -56, 46
	C3	699	Juxtapositional Lobule (Supplementary Motor Cortex) /	5.49	-6, 4, 54
	C2	615	Frontal pole (R)	4.42	46, 58, -2
	C1	545	Middle temporal gyrus (R)	4.52	62, -36, -12
Anger	C5	29'856	Occipital fusiform, temporal occipital, lateral occipital, occipital pole	7.22	-40, -56, -20
	C4	1'486	Parietal (superior parietal lobule), angular gyrus (R)	5.61	32, -54, 44
	C3	1'479	Parietal (superior parietal lobule), angular gyrus (L)	4.79	-28, -52, 40
	C2	942	Juxtapositional Lobule (Supplementary Motor Cortex)	5.11	-6, 4, 54
	C1	517	Cerebellum (R)	3.78	20, -48, -38

Figure 4-1. BOLD activation in all subjects in response to A) all faces, B) fearful faces, C) happy faces, and D) angry faces (all versus fixation).



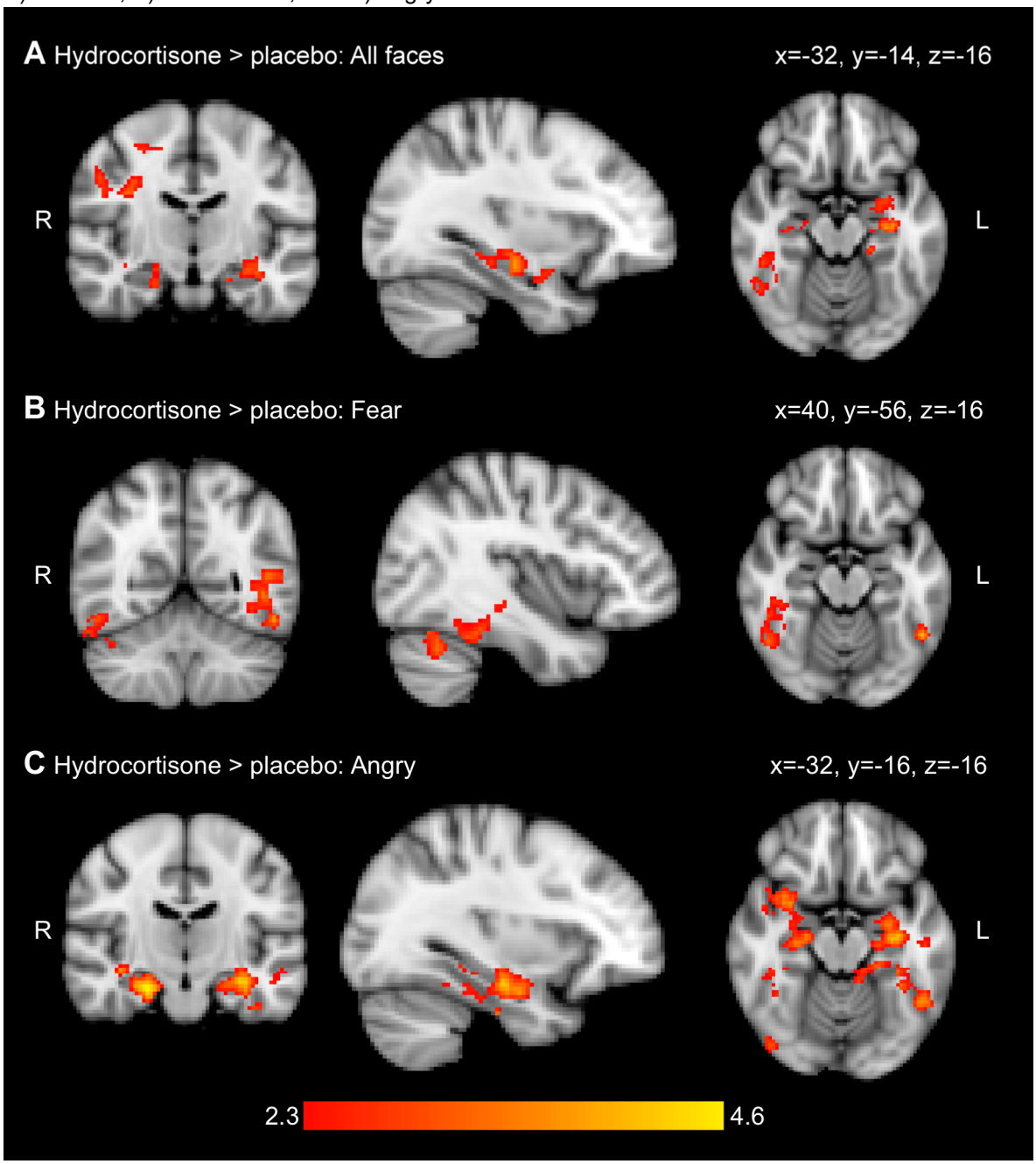
4.3.1.3. Hydrocortisone vs. placebo: Whole-brain analysis

When contrasting BOLD signal between the groups for all faces, the hydrocortisone group showed significantly increased activation in the hippocampus, temporal and temporal fusiform gyri, and somatosensory cortex compared to the placebo group. The most pronounced group differences were seen in response to angry faces, which elicited stronger BOLD activation for participants receiving hydrocortisone compared to those receiving placebo in a number of brain regions (see **Table 4-3** and **Figure 4-2**). These included clusters in the anterior hippocampus and temporal gyrus, extending into the amygdala and temporal fusiform gyrus, and a lateralised cluster in the right lateral occipital cortex. Fearful faces elicited increased BOLD activation in the hydrocortisone group in regions partially overlapping with those for anger, including the inferior temporal and temporal fusiform gyri. Increased hippocampal activation in response to fearful faces was restricted to the right posterior hippocampus only. There were no group differences in BOLD for happy faces, suggesting the contrast for all faces was driven by group differences in response to angry and fearful stimuli.

Table 4-3. Overview of BOLD clusters for increased activation in the hydrocortisone vs. placebo group for emotional faces. Hydrocortisone increased activation for fearful and angry, but not happy, faces compared to placebo. L=Left hemisphere, R=Right hemisphere.

Emotion	Cluster	# of voxels	Brain regions	Max. z	Peak (x, y, z)
Fear	C2	600	Inferior temporal gyrus, temporal occipital / middle temporal (R)	3.66	42, -60, -30
	C1	507	Inferior temporal gyrus, temporal occipital / middle temporal (L)	3.95	-50, -54 -16
Anger	C3	1388	Hippocampus (L), Amygdala (L), temporal fusiform (L)	4.22	-30, -16, -18
	C2	1058	Hippocampus (R), amygdala (R)	4.60	22, -14, -22
	C1	442	Inferior lateral occipital (R)	4.01	56, -70, 2

Figure 4-2. Increases in BOLD signal in participants receiving hydrocortisone vs. placebo. A) all faces, B) fearful faces, and C) angry faces.



ROI analysis

Repeated measures ANOVAs with treatment group and sex as between-subjects factors, and valence and hemisphere as within-subjects factors did not show any overall group differences in BOLD activation between groups in the amygdala ($F(1,32)=0.87$, $p=0.36$), hippocampus ($F(1,32)=0.53$, $p=0.471$), or thalamus ($F(1,32)=0.028$, $p=0.87$). This was in contrast to the whole-brain analysis, which yielded increased hippocampal and amygdala BOLD in participants receiving hydrocortisone vs. placebo.

4.3.2. FERT emotion classification

4.3.2.1. Accuracies

A repeated-measures ANOVA on the classification accuracy of emotional faces showing one of 7 emotions (sadness, fear, disgust, anger, neutral, happy, surprise) revealed a significant interaction effect between group and sex ($F(1,32)=6.76$, $p=0.014$; Greenhouse-Geisser corrected; see **Figure 4-3**). There was also a significant main effect of valence ($F(3.57, 114.06)=15.55$, $p<0.001$). The main effects of group ($F(1,32)=1.00$, $p=0.32$) and sex ($F(1,32)=1.85$, $p=0.18$), and all further interaction effects were non-significant (all p's>0.1).

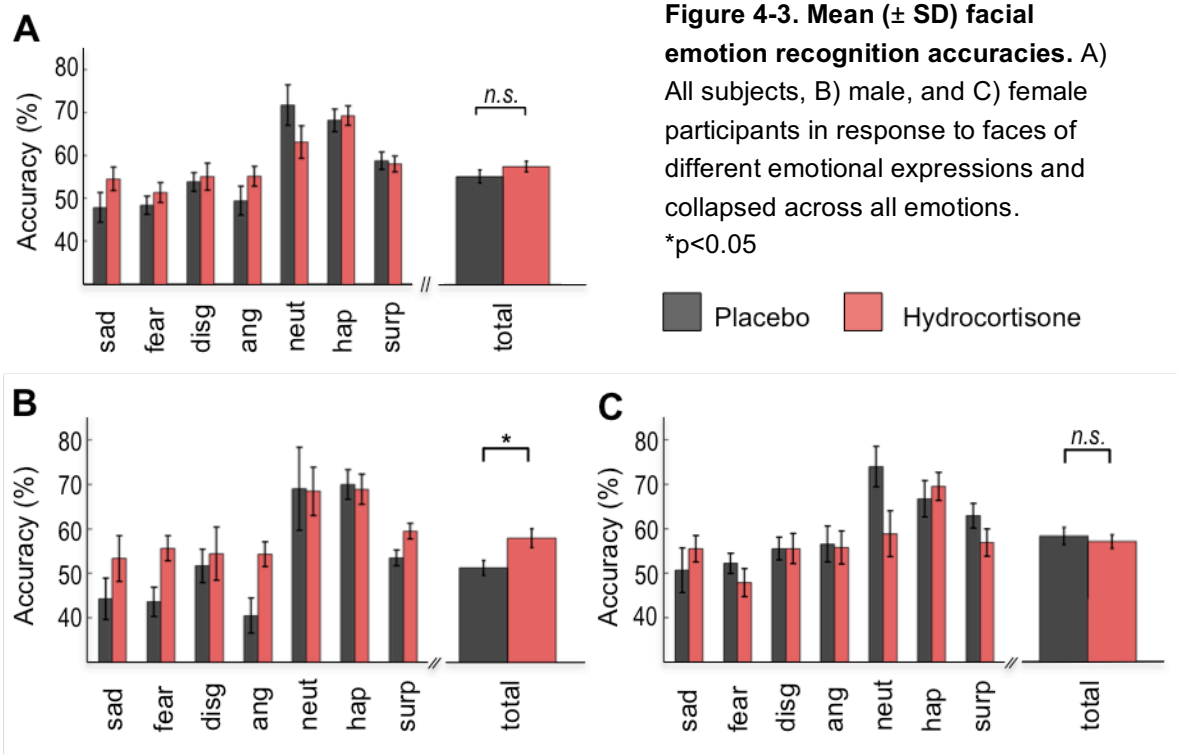


Figure 4-3. Mean (± SD) facial emotion recognition accuracies. A) All subjects, B) male, and C) female participants in response to faces of different emotional expressions and collapsed across all emotions. *p<0.05

The significant group by sex interaction was followed up with independent t-tests for accuracies for male and female participants separately. Accuracy scores collapsed across all emotions revealed that male participants in the placebo group performed significantly worse than male participants in the hydrocortisone group (placebo mean ± SD = 51.41 (4.83) vs. hydrocortisone mean ± SD = 58.13 (6.02), $t(14)=-2.47$, $p=0.027$), whereas female participants did not differ in their overall performance across treatment groups (placebo mean ± SD = 58.17 (6.15) vs. cortisol mean ± SD 56.98 (SD=4.85), $t(18)=0.48$, $p=0.64$). Males performed worse than females in the placebo group

(t(16)=-2.54, p=0.022), whereas males' performance did not differ from females' in the hydrocortisone groups (t(16)=0.45, p=0.66).

4.3.2.2. Reaction times

Repeated-measures ANOVA on reaction time data revealed similar effects to the accuracy data (**Figure 4-4**). There was a significant main effects of valence (F(6,192)=17.46, p<0.001), group (F(1,32)=1.50, p=0.23), and sex (F(1,32)=1.19, p=0.28) were non-significant. However, there was a significant group by sex interaction (F(1,32)=4.76, p=0.037), with all further interaction effects non-significant (p's>0.1 in all cases).

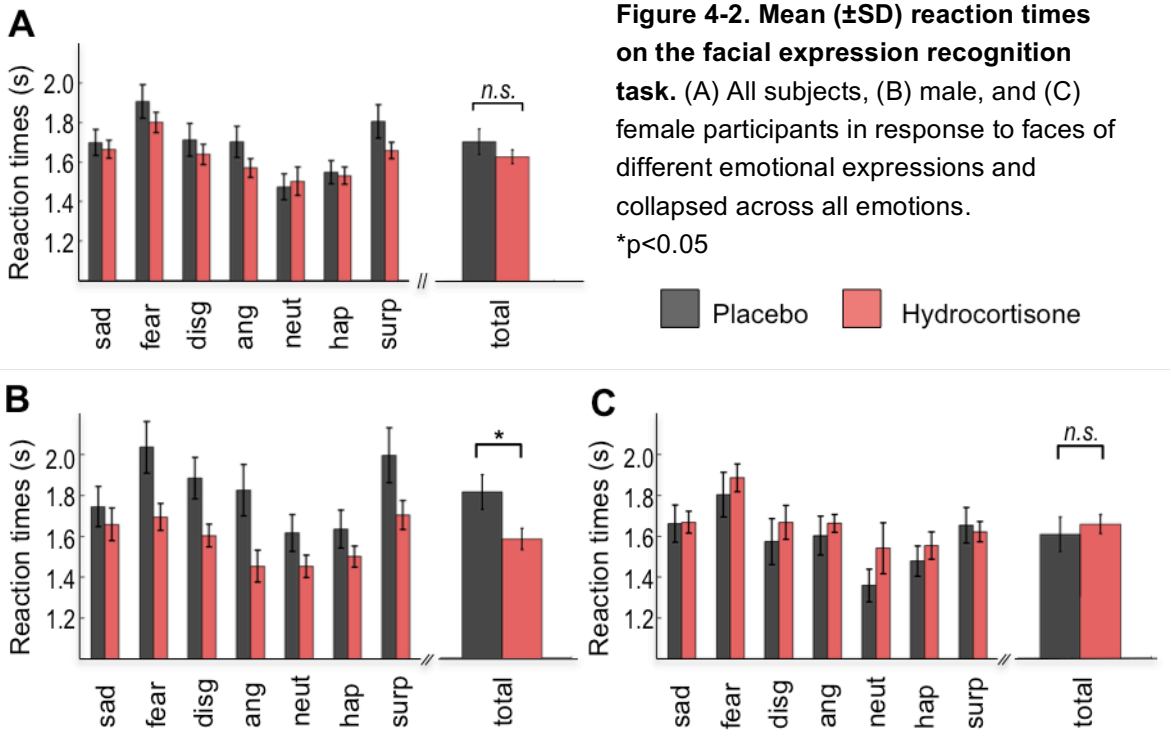


Figure 4-2. Mean (±SD) reaction times on the facial expression recognition task. (A) All subjects, (B) male, and (C) female participants in response to faces of different emotional expressions and collapsed across all emotions.
*p<0.05

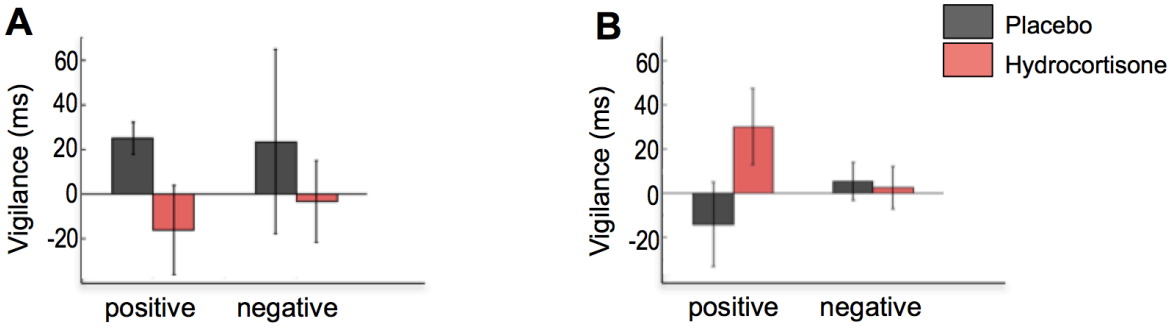
Independent t-tests comparing reaction times in the placebo vs. hydrocortisone groups for male and female participants separately revealed that males in the placebo group responded to faces significantly slower than males in the hydrocortisone group (placebo mean ± SD = 1817 ± 240 ms vs. hydrocortisone mean ± SD = 1586 ± 147 ms); t(14)=2.32, p=0.036). There was no group difference in reaction times in the female participants (PLAC mean ± SD = 1605 ± 268 ms) vs. CORT mean ± SD = 1655 ± 147 ms; t(18)=-0.51, p=0.62). Reaction times for males vs. females

did not differ significantly in either the placebo (t(16)=1.74, p=0.10) or hydrocortisone (t(16)=-0.97, p=0.34) groups.

4.3.3. Attentional dot probe task

A repeated measures ANOVA on vigilance scores revealed no significant main or interaction effects of group (F(1,32)=0.25, p=0.62), sex (F(1,32)=0.27, p=0.61), valence (F(1,32)=0.00, p=0.99), or masking condition (F(1,32)=0.01, p=0.93; see **Figure 4-5**). All interaction effects were non-significant (in all cases p>0.08).

Figure 4-5. Attentional dot-probe vigilance. Vigilance to positive vs. negative words in the (A) masked and (B) unmasked conditions.



4.3.4. Continuous Flash Suppression task

4.3.4.1. Accuracies

A repeated measures ANOVA on response accuracy (indicating the location of a masked face within a square) revealed a main effect of valence (F(2,62)=7.04, p=0.002), driven by a difference in accuracies between neutral and happy faces (paired contrast F(1,31)=7.75, p=0.009; see **Table 4-4**). The main effects of treatment group (F(1,31)=0.22, p=0.64), the interaction between valence and group (F(2,62)=1.05, p=0.36), and all further interaction effects (all p's>0.4) were non-significant. The main effect of sex was at trend (F(1,31)=3.51, p=0.07), with higher accuracies for male participants (mean = 98.85, SD=2.64) compared to female participants (mean=96.78, SD=3.69).

Table 4-4. Mean (±SD) response accuracies and reaction times to detect masked faces with neutral, happy, and fearful emotional expressions in the CFS task. Responses to fearful faces were faster than those to neutral or happy faces, and responses to happy faces were slower than responses to neutral faces.

Measure	Emotion	Placebo	Hydrocortisone
Accuracy (%)	Neutral	96.57 (1.78)	96.11 (4.50)
	Happy	95.49 (2.75)	94.44 (2.75)
	Fearful	96.47 (3.00)	96.76 (4.18)
RT (ms)	Neutral	2804.20 (747.02)	3020.77 (871.63)
	Happy	2933.59 (839.10)	3123.65 (942.50)
	Fearful	2728.56 (740.16)	2895.83 (781.82)

4.3.4.2. Reaction times

Reaction time values revealed a main effect of valence (Greenhouse-Geisser corrected: $F(1.52, 47.10)=9.04$, $p=0.001$; see **Table 4-4**). Participants were faster to respond to fearful than to neutral ($p=0.05$) and happy ($p=0.005$) faces, and slower to respond to happy than to neutral ($p=0.05$) faces. The main effects of group ($F(1,31)=0.46$, $p=0.51$) and sex ($F(1,31)=1.81$, $p=0.19$), and all interaction effects (all p's>0.19) were non-significant.

4.4. Discussion

4.4.1. Overview

This chapter sought to delineate the effects of sustained elevations in cortisol on the attention to, and perception and recognition of, emotional stimuli in healthy volunteers. We found that hydrocortisone administration increased neural correlates of viewing emotional facial expressions in occipital cortex and, for faces displaying anger, in limbic-temporal areas, in the absence of behavioural effects. In a separate task, male participants who had received hydrocortisone showed higher categorisation accuracies of facial emotions compared to males receiving placebo, with no differences in female participants. These effects suggest that sustained increases in cortisol are associated with increased neural correlates of processing emotional – particularly, negative – stimuli, but that the effects of such increases on behaviour depend on task characteristics and gender.

4.4.2. Increases in BOLD during viewing of negative faces

4.4.2.1. Increased threat processing in hippocampus

Our primary finding of interest was a substantial increase in BOLD activation in response to angry faces after repeated hydrocortisone versus placebo intake. These group differences were localised in the anterior hippocampus, extending into adjacent temporal regions and the basolateral amygdala bilaterally. Conversely, there were no group differences in the behavioural (accuracy or reaction time) responses to the concurrent gender categorisation task.

Although best known for its critical role as a structure for learning and memory (Squire et al., 2004), the hippocampus is also known to respond to emotion (see e.g. Kemp & Felmingham, 2008; Phan, Wager, Taylor, & Liberzon, 2002). Specifically, the loci of cortisol-induced group differences are in line with studies reporting hippocampal responses to the viewing (Britton, Taylor, Sudheimer, & Liberzon, 2006) and encoding (E. E. Nelson et al., 2003) of emotional faces. Theories of hippocampal affective processing have particularly highlighted its ability to mediate attention and arousal to stimuli requiring a resolve of conflict for action selection and future learning (Bach et al., 2014; Bannerman et al., 2014; Buchanan et al., 2009; A. C. Chen & Etkin, 2013; Kjelstrup et al., 2002). Previous associations suggest that intact hippocampal structure and function are a necessary component of subjective anxiety and fear conditioning (Adhikari, Topiwala, & Gordon, 2010; Kjelstrup et al., 2002), and are associated with increased trait and state anxiety in humans (Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001; Satpute, Mumford, Naliboff, & Poldrack, 2012).

These findings support the notion that hippocampal processes alter arousal and behavioural aspects of anxiety, for example, through the inhibition of active responses to aversive stimuli (Strauss et al., 2005) and interaction with the medial PFC (Adhikari et al., 2010). In the current study, however, cortisol-induced increases in hippocampal BOLD activation were more widespread for angry faces and less pronounced in response to fearful faces. These selective alterations for angry faces may be linked to the clear antagonistic nature of the stimuli leading to stronger arousal and a

stronger demand for appropriate action selection (Bannerman et al., 2014; Strauss et al., 2005). Although hypothetical, this interpretation is generally consistent with cortisol's wider role in confrontational aggression (Böhnke, Bertsch, Kruk, Richter, & Naumann, 2010; Montoya, Terburg, Bos, & van Honk, 2012; Putman & Roelofs, 2011; Terburg, Morgan, & van Honk, 2009).

While memory and emotional processing in the hippocampus likely show substantial functional commonalities (Buchanan et al., 2009; A. C. Chen & Etkin, 2013), rodent studies have suggested an anatomical dissociation between hippocampal regions, localising declarative memory functions to dorsal (posterior in humans and primates), and affective – particularly anxiety and threat – processing to ventral (anterior in humans and primates) regions (Bannerman et al., 1999, 2003, 2004, 2014; Fanselow & Dong, 2010; Kjelstrup et al., 2002; Moser & Moser, 1998; Sasaki et al., 2004). A small number of studies have tested for this functional long-axis dissociation of the hippocampus in humans (A. C. Chen & Etkin, 2013; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Poppenk & Moscovitch, 2011; Royer, Sirota, Patel, & Buzsaki, 2010), with some support for the anterior hippocampus modulating subjective state anxiety (Adhikari et al., 2010; Satpute et al., 2012). Pronounced increases in anger processing following hydrocortisone in the current study were also localised in the anterior hippocampus, thus supporting a glucocorticoid-mediated role of the hippocampus in the processing of negative, threatening stimuli, which may more specifically be dependent on anterior hippocampal connectivity with the amygdala and medial PFC (Cenquizca & Swanson, 2007; A. C. Chen & Etkin, 2013; Kishi, Tsumori, Yokota, & Yasui, 2006).

4.4.2.2. Cortisol-associated increases in BOLD extend to the amygdala

Weaker group differences extended into the amygdala, where cortisol exerts strong physiological effects (Karst et al., 2002, 2010; Mitra & Sapolsky, 2008), and which shows high functional connectivity with anterior regions of the hippocampus (Cenquizca & Swanson, 2007; Kishi et al., 2006; Parent, Wang, Su, Netoff, & Yuan, 2010; Roy et al., 2009). The amygdala has been extensively studied with regards to its response to emotional salience and stimuli with potential and actual biological relevance (e.g. Breiter et al., 1996; Hesse et al., 2016; Whalen, 2001; for reviews and meta-analyses, see Armony, 2013; Cardinal, Parkinson, Hall, & Everitt, 2002; Costafreda,

Brammer, David, & Fu, 2008; Janak & Tye, 2015; Kober et al., 2008; Lindquist & Barrett, 2012; Murray, Brosch, & Sander, 2014; Pessoa & Adolphs, 2010; Phan et al., 2002; Sergerie et al., 2008). Crucially, its ability to highlight novel (Wright, Wedig, Williams, Rauch, & Albert, 2006) stimuli and those of uncertain predictive value (see e.g. Barrett et al., 2007), is associated with increases in attentional resource allocation to allow enhanced learning relevant to subsequent encounters (see e.g. Kober et al., 2008), habituating quickly once the predictive value of a stimulus has been established (Breiter et al., 1996; Fischer et al., 2003; Sabatini et al., 2009; Sergerie et al., 2008). Overall, our findings of increased BOLD to angry faces in the amygdala following hydrocortisone are in line with this body of literature (Buades-Rotger et al., 2016; Langenecker et al., 2012; Sudheimer et al., 2012), however, the comparatively limited glucocorticoid effects on the processing of negative faces in the amygdala may have been due to habituation effects or specific localisation of effects to amygdalar subregions.

4.4.2.3. Lack of ROI effects and interim conclusion

Given the effects seen in the whole-brain analyses, the lack of group differences in the ROI analyses of MTL regions were somewhat puzzling. However, it may be that due to aspects of the analysis, such as the resolution of the magnetic resonance images, segmentation procedures, or smoothing kernel, the ROI analysis failed to detect cortisol effects in limbic-temporal areas. This may be particularly likely given the large number of subcomplexes in these regions, which contain distinct structural and physiological properties across closely neighbouring topographical sites (Entis, Doerga, Barrett, & Dickerson, 2012; Qin et al., 2014). Across these regions, cortisol may have had effects of varying strength and direction (Gunduz-Bruce et al., 2007; L. R. Johnson, Farb, Morrison, McEwen, & Ledoux, 2005; Sharvit, Segal, Kehat, Stork, & Richter-Levin, 2015; Toffanin et al., 2011), which could have contributed to a lack of reliable group effects. Furthermore, our ROI analysis may have included insufficient voxels from the whole-brain cluster due to its localisation very close to transition areas between the amygdala and hippocampus.

Extensive empirical evidence is needed to investigate the exact roles of the amygdala in biologically salient novelty detection, and the hippocampus as a time-sensitive evaluative

"comparator system". However, the above account of amygdala and hippocampus underlying initial evaluation of affective learning environments (Bannerman et al., 2014; A. C. Chen & Etkin, 2013), particularly those of potential biological significance (Almeida, van Asselen, & Castelo-Branco, 2013; Armony, 2013), may form a good development from previous theories of simple threat processing and memory formation, and can account for some of the inconsistencies found in the literature (see Phan et al., 2002; Sergerie et al., 2008). While the role of hippocampal-amygdalar regions in threat and affective processing, arousal, and anxiety remains a vast area of active study, a potential interpretation of these results is that glucocorticoid mechanisms in the anterior hippocampus and amygdala have the ability to specifically increase the processing of threat-related stimuli in order to adjust attentional and arousal processes as a basis for appropriate action selection and learning.

4.4.2.4. Temporal & occipital-visual BOLD increases for negative faces

Following repeated hydrocortisone administration, participants also showed increases in BOLD in the inferior and medial temporal (including the temporal fusiform) gyri bilaterally during the processing of fearful and angry faces, and increases in the inferior occipital cortex for angry faces only. These areas underlie the perception of visual stimuli as part of the ventral visual stream (Graham et al., 2010a), and have consistently been shown to activate preferentially for faces and other stimuli of emotional salience compared to neutral materials (Critchley et al., 2000; Kober et al., 2008; Sabatinelli et al., 2014; Sabatini et al., 2009; Satpute et al., 2015; Van den Stock et al., 2011). Modulation of these areas by repeated direct administration of cortisol is in line with increases in attentional vigilance of threatening stimuli as evidenced after acute stress (Henckens, Klumpers, et al., 2015; Van Honk et al., 2003; Vogel et al., 2014) and is strikingly congruent with areas found to be enhanced during encoding of negative stimuli in adolescents with depression (R. J. Holt et al., 2016), but has, to our knowledge, not previously been shown for similar manipulations (cf. Sudheimer et al., 2012).

The fusiform face area (FFA; Kanwisher & Yovel, 2006) is also closely linked with the occipital cortex, which forms an integral part of face processing (Rossion et al., 2003). Cortisol-induced

increases in inferior occipital cortex in response to angry faces in the current study thus suggest the HPA axis may influence early sensory input regions. Furthermore, regions of the ventral visual stream including the occipital and occipital temporal lobes as well as the fusiform have shown functional alterations in response to both negative and neutral stimuli following other types of experimental manipulations (e.g. pain - Bingel, Rose, Gläscher, & Büchel, 2007; oxytocin - Liu et al., 2015). Speculatively, these effects may be due to efferent pathways from the amygdala providing affective modulation of the visual cortex, vital for attention and salience, and such pathways may be highly susceptible to context-specific modulation by distinct neurochemical mechanisms.

An active debate concerns the existence of an amygdala-mediated subcortical pathway for rapid detection of emotionally salient stimuli. This suggested functional path has been linked to a colliculus-thalamo-amygdalar route of particularly rapid and early, albeit coarse, signalling pathway for the processing of faces and other salient emotional stimuli (see Garvert, Friston, Dolan, & Garrido, 2014). One possibility, albeit speculative, is that the increased hippocampal and/or amygdalar activation in conjunction with increased BOLD activation in occipito-visual cortices evident following repeated hydrocortisone administration is due to cortisol-induced increases in amygdalar and hippocampal detection of basic signals of "predictive significance" (e.g. such as eye-whites; Whalen, 2004), thus altering a ventral pathway for the rapid detection of the emotionally most relevant stimuli, in this case anger. Given wider criticisms of the "fast-route" hypothesis, it may thus be more fruitful to consider alterations in visual processing areas as part of wider, conceivably MTL-mediated, network changes (Pessoa & Adolphs, 2010). Future pharmacological studies could include functional connectivity analyses to shed further light on potential modulatory influences of cortisol and different types of stress on the emotion- and context-dependent interactions between these regions.

4.4.3. Motivational salience & valence specificity

4.4.3.1. Increased threat vigilance

Enhanced neural correlates of negative face processing are largely consistent with extensive evidence for the role of stress in heightening the processing of stimuli relevant for immediate coping, which involves an increased need to attend to motivationally salient, particularly threatening, stimuli (De Kloet et al., 2005; Ellenbogen et al., 2002; Henckens et al., 2012; Joëls & Baram, 2009; Oei et al., 2011; Putman & Roelofs, 2011). Cortisol's specific role in the processing of threat-related stimuli has largely been studied within the contexts of the acute stress response or long-term HPA axis abnormalities, with little direct findings from repeated pharmacological investigations. Previous studies have found acute cortisol administration to increase biased processing of angry faces in humans (Putman, Hermans, & van Honk, 2007), with the suggestion that cortisol may alter processing of negative social stimuli in part to regulate behavioural avoidance. Within the framework of motivational approach and avoidance mechanisms (see Mogg et al., 2000; Mogg & Bradley, 1998), differential responses induced by angry faces compared to fearful faces are indeed thought to be mediated by endogenous cortisol and testosterone (Roelofs, Elzinga, & Rotteveel, 2005; Stanton, Wirth, Waugh, & Schultheiss, 2009). Interestingly, previous research has found that cortisol (40mg administered acutely) altered the processing of negative stimuli from fearful to angry in healthy males, inducing a (spatial working) memory bias for angry facial expressions while attenuating a bias for fearful faces relative to placebo (Putman, Hermans, & van Honk, 2007).

4.4.3.2. Valence specificity

The specific BOLD increases during processing of angry faces is in line with hydrocortisone showing valence-specific mechanisms for anger, although we also found slight increases in BOLD during processing of fearful stimuli compared to fixation. Anger has been suggested to be a clearer negative signal than fear due to a conceptual distinction regarding the ability to locate the source of threat in the anger stimulus itself whereas for fearful faces, the source of threat is not known (Whalen, 2004; Whalen et al., 2001). Within social contexts, previous findings suggest that biases

of preferential anger processing are reflective of agonistic approach motivation (Carre, Fisher, Manuck, & Hariri, 2012; Krieglmeyer & Deutsch, 2013). This is thought to be partially mediated by low baseline levels cortisol coupled with acute cortisol increases, whereas prolonged glucocorticoid increases have been associated with chronic social defeat and submission (Montoya et al., 2012; Sapolsky, 1994, 1995). However, these findings have largely emerged from studies in animals, including primates, and require further corroboration and comparison in humans, especially given the difficulty in differentiating mechanisms of different negative emotions. For example, repeated hydrocortisone administration in healthy humans was recently found to alter processing of sad faces, without comparable effects on fearful stimuli (Sudheimer et al., 2012). While some generalisations can be drawn based on the large amount of overlap in neural substrates underlying the processing of negative emotions (Kober et al., 2008), these findings point to the importance of future studies to expand on the scarce evidence delineating the full spectrum of negative valences in order to allow for direct comparisons regarding cortisol's specificity and further implications for adaptive behaviours.

4.4.3.3. Higher emotion recognition following hydrocortisone vs. placebo in male participants

We furthermore found differences in emotion categorisation accuracies and reaction times on an emotional facial expression recognition task completed outside of the scanner. Males in the hydrocortisone group performed better (showing higher accuracy rates, and marginally faster response times) than their placebo counterparts, which visually appeared to be more pronounced for negative emotions (sadness, fear, anger) although there was no interaction effect with valence. This effect was contrary to a previous study in patients with Cushing's Syndrome which found decreased accuracy rates for negative faces (Langenecker et al., 2012). This may be due to the chronic, maladaptive nature of cortisol increases in patients with Cushing's disease, in contrast to our comparatively short-term increases in a healthy sample.

4.4.4. Conclusions & Implications

Overall, our findings of increased neural processing of angry and fearful faces are in line with studies that show enhanced neural processing of negative facial stimuli following glucocorticoid interventions (Buades-Rotger et al., 2016; Sudheimer et al., 2012). As in the neutral memory task discussed in Chapter 3, we found that hydrocortisone altered processing of stimuli in the hippocampus. However, these effects differed in their precise localisation and were in the opposite direction (increased BOLD in anterior hippocampus) compared to the neutral memory task activation differences (decreases in parahippocampal BOLD). Overall, repeated cortisol administration showed no discernible effects on behavioural responses requiring fast attentional processing of emotional faces or valenced words, although there were some gender-based differences between the groups. The lack of strong behavioural effects may be due to either glucocorticoid mechanisms or to limited sensitivity of the tasks to the pharmacological intervention, given findings of altered neural correlates. Furthermore, previous research using the attentional dot-probe task suggests the task may be more sensitive in detecting clinically relevant differences in negative processing when using facial stimuli (Pishyar et al., 2004), which indicates our use of verbal stimuli may underlie the lack of group effects in this task. On the facial expression perception task, cortisol affected emotional attention most strongly for angry faces, and the lack of anger-specific stimuli in either the CFS or the dot-probe may have contributed to a lack of sensitivity in detecting pharmacological effects. A shortcoming of our design was the inclusion of a limited range of emotions (fearful, angry, and happy faces) due to time constraints, therefore foregoing the ability to specifically compare results directly with the study most similar in design to ours (Sudheimer et al., 2012; published after finalisation of our study protocol).

Our results suggest that the modulation of emotional processing biases by prolonged glucocorticoids remains an area of fruitful investigation, albeit one hampered by methodological difficulties. Further studies are required to further characterise the specificity of glucocorticoid effects in both healthy and patient studies. Importantly, our results have so far revealed good sensitivity of BOLD to the pharmacological effects of cortisol, particularly in the temporal and

occipital lobes. However, neuropsychiatric disorders have also been associated with altered functional connectivity between brain areas as investigated with resting-state fMRI, and such general changes in brain metabolism may also be evident following hydrocortisone administration. The subsequent chapter therefore investigates the impact of sustained cortisol increases on resting-state functional connectivity based on the sample of healthy participants receiving either 10-day hydrocortisone or placebo.

CHAPTER 5: EFFECTS OF REPEATED HYDROCORTISONE ADMINISTRATION ON RESTING-STATE CONNECTIVITY

5.1. Introduction

5.1.1. Overview

So far, we have seen that repeated hydrocortisone administration in healthy volunteers was associated with decreased parahippocampal activation during neutral memory processing, enhanced declarative memory for positive and negative words, and increased neural correlates of negative face processing. These neural and behavioural findings were found in addition to gender-dependent increases in negative affect. Given previous evidence of altered resting-state functional connectivity (rsFC) in stress-related disorders and following cortisol manipulations, potential non-task related changes in intrinsic functional connectivity patterns following sustained increases in cortisol are important to delineate as they may contribute to our understanding of neural mechanisms underlying pharmacological manipulations and in patients with hypercortisolaemia. We therefore acquired MR images of resting-state BOLD activation to allow for analysis of rsFC following repeated administration of hydrocortisone in healthy volunteers.

5.1.2. Rationale for resting-state functional connectivity

MRI investigations of the brain at 'rest', i.e. when not focussing on task performance, are based on the premise that low-frequency (0.01-0.1Hz) fluctuations in cerebral haemodynamics are able to dissociate neuronal activity from other physiological and blood-vessel activity (C. F. Beckmann, DeLuca, Devlin, & Smith, 2005; C. F. Beckmann et al., 2005; Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). On the basis of correlated temporal dynamics in grey matter, a number of underlying connectivity patterns that form reliable resting-state networks (RSNs) with good replicability and

spatial consistency across studies have been identified using model-free independent component analysis (ICA; C. F. Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006). Alternative model-based approaches using seed-based connectivity analyses (SCAs) have investigated rsFC patterns from predefined anatomical regions of interest based on a priori hypotheses (e.g. A. C. Chen & Etkin, 2013; L. A. Kilpatrick, Zald, Pardo, & Cahill, 2006; van Marle et al., 2010). The recent extensive use of both methodologies has resulted in progressively detailed descriptions of altered functional connectivity patterns in relation to psychiatric disorders (e.g. Anand et al., 2009; Lui et al., 2014; Mulders et al., 2015; Pannekoek et al., 2014)(e.g. Celone ea 2006; Garrity ea 2007), interventions such as pharmacological effects (McCabe & Mishor, 2011; Pflanz et al., 2015) or acute stress (van Marle et al., 2010), and trait and state variables such as negative affect and anxiety (Baur et al., 2013).

5.1.3. Stress- and disease-associated alterations

Specifically, patients with depression have shown alterations across a number of RSNs, such as the default-mode network (DMN; Kühn & Gallinat, 2013)(DMN; Kühn & Gallinat, 2013), central executive network (CEN), and areas underlying salience processing (see Mulders et al., 2015; Northoff, Wiebking, Feinberg, & Panksepp, 2011). The DMN, also labelled the "task-negative" network due to its activation during baseline conditions and internally directed cognition, includes the posterior cingulate cortex, medial prefrontal cortex, and parts of the hippocampal formation (Greicius et al., 2003; Raichle et al., 2001). DMN dysfunction has been shown across a range of psychiatric disorders (Broyd et al., 2009b; Greicius et al., 2007), and adults exposed to early life adversity have also shown reduced DMN connectivity in anticipation of a stressor (Sripada, Swain, Evans, Welsh, & Liberzon, 2014). At times found to be anti-correlated to the DMN (Sridharan, Levitin, & Menon, 2008), the CEN is thought to be in cognitive control functioning, decision-making, and integration of information from the external environment, and includes the prefrontal cortex, particularly the dorsolateral PFC, and lateral parietal cortex (Seeley et al., 2007; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Alterations in the rsFC of the central executive, and more generally, areas of the PFC, have been shown repeatedly in those at risk of, suffering from, or

remitted from depression, with lower prefrontal connectivity sometimes associated with worse clinical and functional outcomes (Anand et al., 2009; Huang et al., 2014; Rao et al., 2016; Salomons et al., 2014; see Dichter et al., 2015). Finally, a network including the dorsal anterior cingulate and frontoinsular cortices, labelled the salience network (SN), has shown robust connectivity with limbic structures and abnormalities in both depressive and anxiety disorders (Pannekoek et al., 2014; Seeley et al., 2007; Sripada et al., 2012; van Tol et al., 2013). Specifically, increased connectivity of regions within the SN has been found in anxiety and depression (Pannekoek et al., 2013, 2014), and following acute stress induction in adults (van Marle et al., 2010) and adolescents (Thomason, Hamilton, & Gotlib, 2011), while decreases in rsFC between amygdala and insula as found in depression may be reflective of an impairment in integrating affective information (Veer et al., 2010). In addition to activating during processes requiring attention and working memory, the SN has furthermore been associated with responses to pain and homeostatic challenges (Seeley et al., 2007).

As outlined, stress-related changes to some extent overlap with regions found to show altered rsFC in depression, and these have been suggested to play a functional role in symptomatic changes (Hall et al., 2015; Philip et al., 2013). Endogenous cortisol levels under stress-free conditions have also been associated with rsFC, with higher levels related to stronger negative connectivity between the amygdala and areas of the medial PFC (Veer et al., 2012). As with functional tasks (Demenescu et al., 2013), abnormal rsFC patterns in depression and anxiety often include the amygdala as a pivotal mediator of wider alterations in neural patterns (Greicius et al., 2007; Hahn et al., 2011; Qin et al., 2014; Ramasubbu et al., 2014), which may be altered by direct glucocorticoid and wider HPA axis effects (Hall et al., 2015; Kiem et al., 2013).

5.1.4. Chapter aims

Given that rsFC is sensitive to drug effects, and previous findings of rsFC alterations following stress manipulations, we sought to identify alterations in resting-state connectivity patterns following repeated hydrocortisone administration. We first performed an independent component

analysis to test for alterations in previously identified networks of rsFC, previously shown to highlight differences of potential psychopathological relevance. However, given our findings in Chapters 3-4 and the extensive modulatory role of the amygdala in the central stress circuitry, we specifically postulated alterations in rsFC from limbic-temporal regions, which are not fully represented in the above RSNs. We therefore conducted additional seed-region to whole-brain connectivity analyses from the amygdala and hippocampus, hypothesising altered functional connectivity with subcomplexes of the frontal cortex and prelimbic areas.

5.2. Materials & Methods

Participants were the same 36 healthy individuals as those described in Chapters 2-4 (20 females and 16 males, with gender groups split evenly across placebo and hydrocortisone administration). Please see Chapter 2 for a full description of the study methodology.

5.2.1. Data acquisition

For the resting-state scan (recorded after acquiring structural and supplementary, but prior to task-related MRI scans), subjects were instructed to lie with their eyes open and think of nothing in particular while staying awake. A whole-brain, single gradient echoplanar imaging (EPI) sequence was used to record BOLD activity (TR = 2000ms, TE=28ms, Flip angle = 89 degrees, FOV = 192mm, voxel size = 3 x 3 x 3.5 mm, 180 measurements, acquisition time = 6 min 4 s). fMRI data was analysed using FSL (version 5.0.9, FMRIB Analysis Group, Oxford University, UK).

5.2.2. Data analysis

5.2.2.1. Independent Component Analysis (ICA) of RSNs

Preprocessing of resting-state data consisted of brain extraction, motion correction, unwarping using the acquired field maps, spatial smoothing using a full-width at half-maximum Gaussian kernel of 6.0 mm, high-pass temporal filtering (150 s; 0.007 Hz), co-registration to individuals' structural image for each subject, and normalisation into standard space using the MNI-152 template. Multivariate Exploratory Linear Optimised Decomposition into Independent Components

(MELODIC) was used to extract components (C. F. Beckmann et al., 2005) by temporal concatenation of functional data across subjects, and principal component analysis for Bayesian dimensionality estimation (C. F. Beckmann & Smith, 2004). The decomposition was restricted to 25 independent components in order to optimise component loading, and thresholded at values of $z>3.0$. The 25 ICs were classified as belonging to previously reported RSNs (C. F. Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Smith et al., 2009) or as physiological or scanner noise. A dual regression yielding subject-specific components from group spatial maps (C. Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009) was performed. The individual participants' maps were then collated into a single 4D file and differences between groups were analysed using voxel-wise nonparametric permutation *t* tests with 5000 permutations (Nichols & Holmes, 2002), using FSL's Randomise. Additionally, sex (demeaned), relative and absolute motion, and grey matter volume were entered as regressors in the group comparison GLM. Between-group differences were mapped as spatial maps corrected for multiple comparisons using threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009 $p<0.05$).

5.2.2.2. Seed-based connectivity analysis

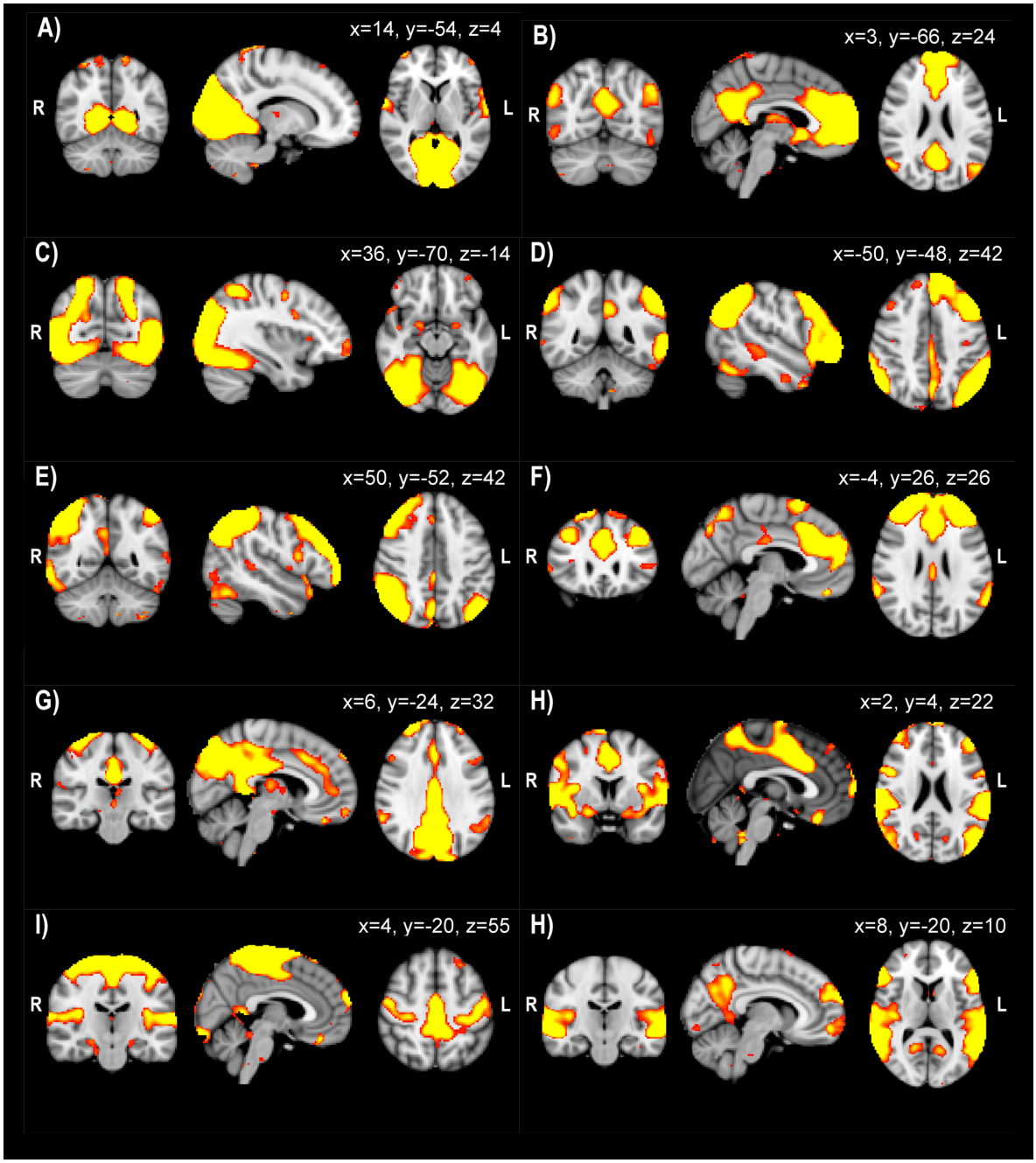
Based on prior hypotheses, masks for the seed regions of interest (ROIs) consisted of the left and right amygdala and hippocampus and were created for each subject from anatomical images based on the Harvard-Oxford subcortical atlas, thresholded at 50%. Following preprocessing, individual fMRI timecourse signal from the seed regions, as well as from manually drawn masks for cerebrospinal fluid and white matter regions, were extracted using FSL Featquery. Time series for the ROI of interest, cerebrospinal fluid, and white matter were averaged across masks, and entered into a multiple regression analysis using the subject-level FSL FEAT function, yielding individual correlation maps of voxels positively or negatively correlated with the seed region. The resulting statistical maps were entered into a group-level GLM contrasting the hydrocortisone and placebo groups, with sex (demeaned), absolute and relative motion, and grey-matter volume as covariates (Woolrich et al., 2004). Images of z-statistics were thresholded using a threshold of $Z>2.3$, and a whole brain family-wise error-corrected cluster significance threshold of $p<0.05$.

5.3. Results

5.3.1. Independent Component Analysis (ICA)

Of the 25 components, 10 were identified as belonging to previously studied RSNs (**Figure 5-1**).

Figure 5-1. Resting state networks identified using ICA. A) Medial visual, B) Default mode-I, C) Lateral visual, D) Frontoparietal-I, E) Frontoparietal-II, F) Central executive, G) Default mode-II, H) Auditory / Sensory-motor / Salience, I) Sensory-motor, J) Auditory



Among these, we identified components belonging to a medial visual, lateral visual, left- and right-lateralised frontoparietal, central executive, default mode, sensory-motor, and auditory networks. The remaining components were classified as artefacts based on physiological and scanner noise. There were no significant differences in functional connectivity maps between the placebo and hydrocortisone groups (all p's > 0.05).

5.3.2. Seed-based

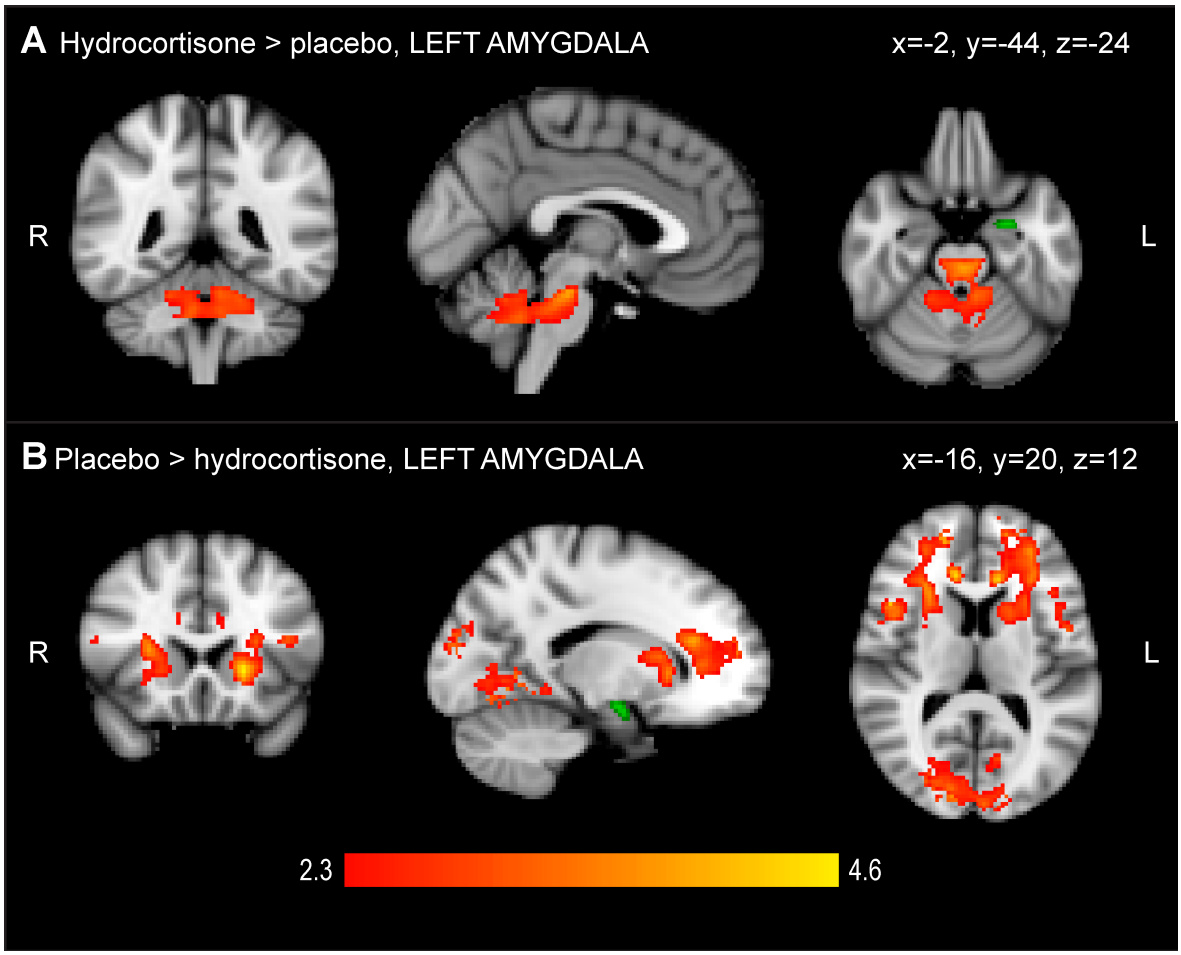
Using the amygdala and hippocampus as seed regions of interest (separately for each hemisphere), we found altered time-course associations with a number of regions between the hydrocortisone and placebo groups (see **Table 5-1**, **Figure 5-2,** and **Figure 5-3**).

Table 5-1. Resting-state functional connectivity differences between the hydrocortisone and placebo groups from the seed regions in the left and right amygdala, and left hippocampus.

Condition	Cluster	# of voxels	Brain regions	Max. z	Peak (x, y, z)
Amygdala (left)					
Placebo > Hydrocortisone	C3	3'058	Right + left lingual gyrus, occipital lobe, occipital pole	4.49	20, -46, -8
	C2	2'213	Left frontal cortex + midbrain: caudate head, putamen, frontal pole, precentral gyrus,	4.46	-20, 20, 0
	C1	1'680	Right frontal cortex + midbrain: caudate head, frontal pole	4.24	12, 32, 12
Hydrocortisone > Placebo	C1	1'970	Cerebellum, brain stem	3.74	0, -26, -22
Amygdala (right)					
Placebo > Hydrocortisone	C3	4'322	Bilateral visual cortex / occipital lobe, lingual gyrus, occipital pole	6.21	16, -86, 14
	C2	1'806	Left frontal: White matter, Putamen / caudate, Frontal pole, Precentral gyrus	4.31	-12, 30, 12
	C1	1'101	Right frontal: White matter, Frontal pole	4.00	12, 32, 14
Hippocampus (left)					
Placebo > Hydrocortisone	C3	9'176	Occipital visual, lingual gyrus, fusiform (bilateral)	5.22	20, -68, -14
	C2	2'860	Left: Putamen / caudate, frontal pole / gyrus, insula, WM (callosal body), somatosensory / opercular cortex	4.74	-20, 20, -2
	C1	2'287	Right: Putamen / caudate, frontal pole / gyrus, insula, WM (callosal body), somatosensory / opercular cortex	4.30	12, 32, 10
Hydrocortisone > Placebo	C1	684	Brainstem, cerebellum	3.51	8, -46, -36

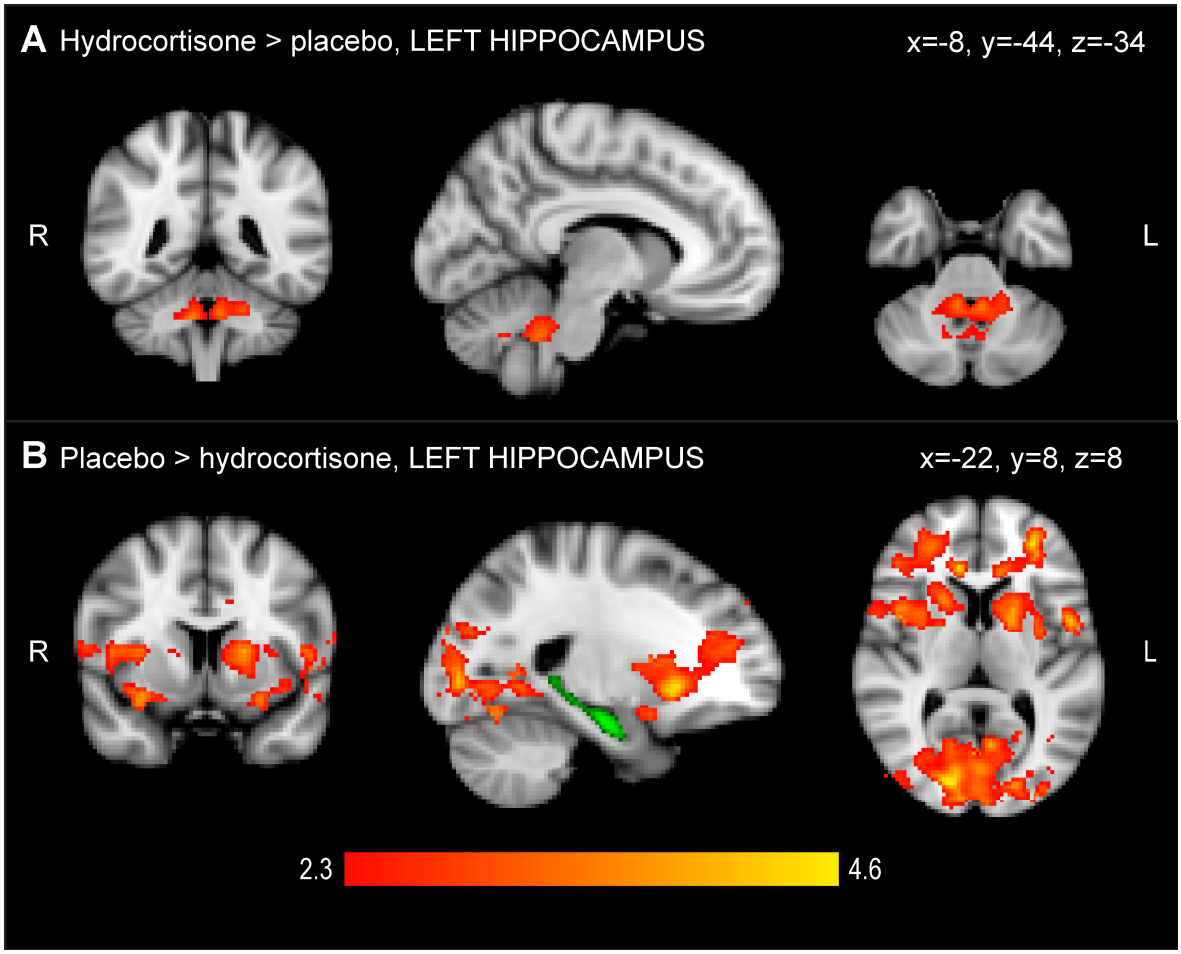
Increased connectivity was evident in the hydrocortisone group between both seed regions and an area of the brainstem extending into the cerebellum. Decreased connectivity patterns were found between the seed regions and the basal ganglia, particularly the caudate. Amygdala/hippocampus were furthermore found to shower lower connectivity with occipital/visual areas in the hydrocortisone vs. placebo group, and frontal areas including the frontal pole, inferior frontal gyrus, and extending into the anterior insula and anterior cingulate cortex.

Figure 5-2. Amygdala seed (green) resting-state connectivity differences between hydrocortisone and placebo groups. A) Placebo > Hydrocortisone B) Hydrocortisone > Placebo. Only images based on left hemisphere seeds are shown due to large overlap.



Connectivity estimates for the amygdala to the above regions were somewhat higher than those for the hippocampus, but the patterns were similar.

Figure 5-3. Left hippocampal seed (green) connectivity differences between participants receiving hydrocortisone vs. placebo. A) Placebo > Hydrocortisone B) Hydrocortisone > Placebo. There were no significant differences in the right hippocampus.



5.4. Discussion

5.4.1. Overview

This chapter examined the impact of non-acute cortisol administration in healthy individuals on neural rsFC. Previously identified resting state networks (RSNs) were replicated using independent component analysis (ICA), but these networks did not show altered connectivity patterns in the hydrocortisone groups compared to the placebo group. Conversely, seed-to-voxel analyses revealed that hydrocortisone administration was associated with decreased functional connectivity between the amygdala and hippocampal seed regions and basal ganglia, insular and frontal regions, as well as occipito-visual areas. Hydrocortisone also increased functional connectivity between limbic-

temporal regions of interest and an area of the brain stem adjacent and extending to the cerebellum. Overall, the current findings of sustained cortisol increases modulating limbic-temporal resting-state connectivity with striatal, frontal, occipital, and brainstem regions extend our knowledge of the HPA axis's extensive effects on neural connectivity at rest.

5.4.2. Model-free network analysis

Despite good validity of our RSNs based on those previously reported in the literature (C. F. Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006), the hydrocortisone and placebo groups showed no differences in connectivity patterns in model-free RSNs. Of particular interest were the DMN (Greicius et al., 2003) and CEN (Vincent et al., 2008), given findings of alterations in depressed patients. Decreases in rsFC patterns have previously been linked with risk status for psychiatric disease as well as acute depression (Broyd et al., 2009b; Northoff et al., 2011). Furthermore, our results are in contrast to studies that have shown stress-related alterations in rsFC between regions corresponding to the salience network (Thomason et al., 2011). Firstly, these discrepancies to previous stress-related alterations highlight the importance of studies investigating the impact of different glucocorticoid manipulations and timecourses on neural connectivity. Furthermore, however, it is possible that the ICA analyses were insufficiently sensitive to detect effects of hydrocortisone, given that the areas we most strongly hypothesised to be altered – particularly the amygdala – were not strongly represented in the RSNs that have been proposed in the literature, and replicated in the current data. Our lack of group differences in these networks may thus be indicative of regionally specific effects of hydrocortisone given the current protocol. In line with this are our findings of opposing effects to neutral and emotional stimuli in areas associated with visual processing in tasks dependent on hippocampal and amygdala function (Chapters 3 and 4). The majority of our findings from previous chapters are thus in line with a strong modulatory effect of these regions on neural processing, suggesting that effects on wider networks may only be evident when these regions are taken into account, which may explain the lack of group differences in temporal or occipital RSNs.

5.4.3. Decreased resting-state functional connectivity with frontal and prelimbic areas

Seed-based connectivity analyses (SCA) confirmed alterations in functional connectivity patterns in response to repeated hydrocortisone. Contrary to our hypotheses, rsFC patterns of the amygdala and hippocampus with cortical regions were not increased in areas of interest such as the PFC and salience network following repeated hydrocortisone. Instead, connectivity patterns with striatal, occipital, paralimbic, and frontal regions were found to be decreased, while increased connectivity between the anatomical seeds was limited to a cluster located in the brainstem and cerebellum.

Brain regions showing decreased functional connectivity included frontal areas including the inferior frontal gyrus and frontal pole, extending into the anterior insula and anterior cingulate cortices. The loci of these alterations are partially congruent with nodes of the salience network previously found to be associated with cognitive performance and subjective anxiety (Seeley et al., 2007; Thomason et al., 2011). Areas of the SN, particularly the insular cortex, are thought to be involved in the continuous processing of interoceptive and emotional awareness, and the monitoring of homeostatic events in order to "guide adaptive behaviour" (Seeley et al., 2007; Thomason et al., 2011; van Marle et al., 2010), and amygdala-insula rsFC has previously been linked to emotional dysregulation (Bebko et al., 2015), and state anxiety (Baur et al., 2013).

The loci of the brainstem alterations resemble reports of altered functional connectivity in the anterior insula and anterior cingulate cortex following an acute stress induction (van Marle et al., 2010), although their acquisition of resting-state images 60 mins following the viewing of highly arousing movie clips yielded an effect of increased connectivity with the amygdala, in contrast to the decreases following repeated hydrocortisone administration. The authors interpreted this as an increase in a network-mediated "background scan for homeostatic salience" (van Marle et al., 2010). Altered glucocorticoid mechanisms due to the repeated increases in cortisol in our study may underlie the opposing different direction of our effects. For example, our repeated pharmacological administration of cortisol may have led to a down-regulation of these effects due

to adaptive or regulatory mechanisms in our healthy study population. Alternatively, or additionally, the differences between these results may be due to the comparatively long time-span since the last induced cortisol increase in our study compared to the recent timing of the previous' study acute stress intervention. Differences in glucocorticoid kinetics and their slow vs. fast-acting physiological effects have previously been shown to exert opposing effects in other settings (Henckens, van der Marel, et al., 2015; Henckens et al., 2010). Acute stress tests – as employed in the study by van Marle and colleagues (2010) – furthermore involve social elements, which have been shown to involve non-glucocorticoid neuromodulators, especially in PFC areas. Such an intervention likely differed from the neuromodulatory effects induced by repeated hydrocortisone intake. Finally, the emotional salience of the task settings in the previous study resulted in different contextual settings of the two studies, possibly contributing to the differences in results, as our resting-state images were acquired prior to any emotional or arousing tasks. This latter interpretation may be particularly relevant given our findings of decreased neutral and increased negative stimulus processing in previous chapters.

Clusters of decreased amygdala connectivity extended into frontal areas including parts of the inferior frontal gyrus and frontal pole. These neural correlates altered by cortisol are partially in line with specific regions of the frontal cortex identified by meta-analyses as showing reliable neural co-activation with subcortical areas in response to emotional tasks. A previous study, which found (acute, cold pressor) stress-induced alterations in functional activity of brain regions including the fusiform face area, posterior areas of visual processing and the inferior frontal gyrus, suggested that the IFG forms part of a neural "action representation circuit" (Mather et al., 2010) that also includes the temporal pole and insula, and is associated with perception, interpretation, and internal representation of emotions. Crucially, the amygdala is thought to form a key node in this circuitry, and may provide a modulatory function given its extensive feedback connections in these areas (Liu et al., 2015). However, some areas of the PFC previously associated with decreased rsFC with the amygdala, and emotional regulation during tasks in the context of stress and psychiatric disorders, such as specific regions of the medial PFC, were not reliably altered by

repeated hydrocortisone. Future research may improve on these findings by dissociating between limbic-temporal and prefrontal subcomplexes, to better capture clinically relevant differences in connectivity between these regions (cf. A. C. Chen & Etkin, 2013).

5.4.4. Decreased limbic-striatal functional connectivity

Furthermore, participants receiving hydrocortisone showed decreased connectivity patterns between the amygdala and hippocampus and an area of the basal ganglia spanning the head of the caudate and extending into the ventral putamen. The basal ganglia is known to play a pivotal role in learning and memory, contributing in particular to reward-based learning strategies (M. X. Cohen & Frank, 2009; Grahn, Parkinson, & Owen, 2009). While the exact roles and connectivity patterns of striatal subregions remain areas of intense study, areas of the caudate are thought to contribute to aspects of both goal-directed behaviour and habit formation (Goode, Leong, Goodman, Maren, & Packard, 2016; Lingawi & Balleine, 2012; Schwabe & Wolf, 2011, 2012). Importantly, the extent of striatal engagement during learning and memory is modulated by stressful contexts, with acute stress usually associated with increased rigid, caudate-based response strategies at the expense of flexible, but cognitively demanding hippocampal-dependent strategies (Kim, Lee, Han, & Packard, 2001; Schwabe et al., 2007, 2008; Schwabe, Schächinger, De Kloet, & Oitzl, 2010; Wingard & Packard, 2008). Although the majority of these studies have investigated effects of acute stress on these processes, increased use of caudate-based versus hippocampal-based learning strategies has also been shown by young adults exposed to prenatal stress compared to a non-exposed group (Schwabe, Bohbot, & Wolf, 2012). These strategies are thought to depend on modulation by the amygdala, and a recent finding of increased task-related connectivity between the amygdala and striatum under stressful contexts provides evidence that MR-availability is required for similar effects (Vogel et al., 2014). Cortisol's MR-dependent action may thus delineate a potential glucocorticoid mechanism underlying the amygdala-modulated enhancement of striatal involvement following acute stress.

Our pharmacological protocol led to reduced amygdala-caudate connectivity, which was in contrast to previous findings of increases in functional task-based connectivity that were found to be dependent on altered MR-availability (Vogel et al., 2015). The ventral caudate and putamen are also involved in the processing and regulation of emotionally salient information, in part due to their functional connectivity with areas of the MTL (amygdala/hippocampus) and prefrontal cortex (Postuma, 2005). Interestingly, a meta-analytic analysis of caudate connectivity found that this functional connectivity extended to areas of the salience network and PFC, including the anterior cingulate cortex, insula, and IFG (Robinson et al., 2012). Broadly consistent with this are findings of altered striatal (in particular, caudate and putamen) structure and function in a variety of psychiatric disorders, which have led to theories that disruptions in striatal reward processing system form a common pathway of impairments across a number of psychiatric disorders including depression, PTSD, and obsessive compulsive disorder (Anticevic et al., 2014; Bennett, 2011; Hall et al., 2015; Herringa, Phillips, Almeida, Insana, & Germain, 2012). While our results were unable to directly test glucocorticoid modulation of striatal action in the context of the above theories, the effects of cortisol on limbic-striatal rsFC indirectly supports the role of glucocorticoids in striatum-mediated abnormalities that may be central to stress-related neuropsychopathologies (see Hall et al., 2015).

5.4.5. Decreased limbic-occipital connectivity

In addition to the alterations in amygdala connectivity with frontal-striatal regions, amygdala/hippocampus showed lower functional rsFC with occipital areas in the hydrocortisone vs. placebo group. These visual processing areas resemble regions showing decreased BOLD during encoding of neutral and increased BOLD during viewing of negative faces in the hydrocortisone group (as discussed in Chapters 3 and 4). Although our initial hypothesis regarding increased vigilance under conditions of increased cortisol levels would suggest an up-regulation of sensory processing following the hydrocortisone manipulation, this effect may be explained in light of the non-emotional context of data acquisition, especially given occipital BOLD decreases during neutral pictures and increases in similar areas during negative face processing in the current

sample. Therefore, these decreased connectivity patterns with the amygdala and hippocampus as seen in the seed-based analysis (but not in RSNs that incorporate these regions) are further in line with the ability of glucocorticoids to modulate temporo-occipital regions via hydrocortisone's effects on the amygdala and hippocampus.

5.4.6. Increased connectivity with brainstem

Increased rsFC was evident in the hydrocortisone group between both the amygdala and hippocampus and an area of the brainstem adjacent to and extending into the cerebellum. Interestingly, our results are highly congruent with a previous finding of increases in rsFC between the amygdala and a region of the brainstem 60 minutes after a stress-induction task (van Marle et al., 2010). The authors tentatively interpreted this as increased noradrenergic activity associated with emotional arousal, as the brainstem area of interest is anatomically corresponding to the location of the locus coeruleus, the main source of noradrenaline release into the brain. Our current results support this stress-induced change in brainstem-limbic coupling but are equally unable to confirm the neurochemical specificity, in particular given its close proximity to other loci of neurotransmitter release. Interestingly, increased amygdala-brainstem rsFC following our repeated hydrocortisone intervention was in the same direction as the connectivity changes following acute social stress, but we found opposing effects in frontal areas including the anterior insula and areas of the salience network. This may suggest that the different manipulations of the HPA axis (repeated hydrocortisone vs. acute stress induction) had similar upregulatory effects on brainstem-limbic interactions, but is equally congruent with context-dependent or compensatory processes resulting in reduced limbic-cortical rsFC as discussed above.

5.4.7. Conclusions & Implications

We found widespread decreases in rsFC between the amygdala and cortical regions including the IFG, striatum, and occipital lobe, but no altered ICA-based RSNs following repeated cortisol administration. To our knowledge, this is the first report of decreased rsFC following repeated hydrocortisone administrations, and these results are partially contrasting those reported following

acute stress manipulations. Speculatively, this may be indicative of lessened processing of neutral materials following 10-day cortisol due to increases in the salience of emotional materials, or constitute a regulatory response to the repeated nature of the pharmacological challenge. Our hippocampal and amygdalar seed regions showed remarkably similar connectivity patterns, with marginally extended patterns of reduced connectivity between the hippocampus and occipital-visual areas. This may be have been due to overlapping roles of these regions in modulating glucocorticoid effects on the rest of the brain, or of comparatively low spatial specificity of our ROIs. Overall, these findings extend previous findings of altered connectivity between similar brain regions following acute stress, and in patients with depression and anxiety. However, future results may be improved with higher-resolution imaging and better segmentation (Robinson et al., 2012; Roy et al., 2009), allowing for greater selectivity and therefore more clear cut interpretations. In contrast to a number of previous studies in the stress literature, our sample included both male and female participants. It is now crucial to conduct studies with increased power to allow for a characterisation of gender-dependent responses to cortisol manipulations, and also to delineate the potential relationships between the resting-state effects and task-based and subjective measures.

CHAPTER 6: MANIPULATING THE HPA AXIS VIA GUT MICROBIOTA

6.1. Introduction

The results from *Study 1*, a pharmacological intervention study in healthy volunteers, confirmed the effects of sustained cortisol increases on negative emotional processing and affect, neutral and emotional memory, and resting-state functional connectivity (presented in Chapters 2-5). The most pronounced effects of hydrocortisone were apparent on emotional memory performance, and on BOLD activation in limbic-temporal regions. The HPA axis in general, and glucocorticoid processes in limbic-temporal regions in particular, are known to have widespread effects on and interactions with wider physiological and peripheral systems. While these complex links pose methodological and experimental challenges for teasing apart the exact functions of cortisol in central and behavioural correlates of psychiatric disease, such systems may also pose useful targets for modulating the HPA axis. We therefore conducted a separate study in healthy volunteers, which aimed to test the potential of gut microbiota alterations on HPA axis responsivity in healthy volunteers, and the perception of, attention to, and interpretation of emotionally salient information.

6.1.1. HPA axis – gut microbiota interactions

The adult human gut microbiota comprises over 1000 species and 7000 bacterial strains and is characterised by a balanced compositional signature with moderate inter-individual variability (Cryan & Dinan, 2012; Gareau, Sherman, & Walker, 2010). Probiotic strains, which have the ability to confer beneficial effects upon the host, have received renewed attention in recent years (Forsythe & Kunze, 2013). A particular focus has been put on their ability to influence neural and endocrine systems and behavioural phenotypes (Cryan & Dinan, 2012; Cryan & O'Mahony, 2011). Their potential influence on the mechanisms underlying stress-related disorders such as irritable bowel syndrome (IBS), anxiety, and depression are also beginning to be elucidated (Bravo et al.,

2012; Dinan et al., 2006; Mayer, 2011; Rhee, Pothoulakis, & Mayer, 2009). Recent findings in rats have demonstrated that prebiotics – oligosaccharides that promote the growth of indigenous beneficial gut bacteria such as *Lactobacilli* and *Bifidobacteria* – also have neurotropic effects (Savignac et al., 2013, 2016), but the central actions of these compounds in humans are still largely unexplored.

Convincing evidence now exists for a role of the gut microbiota composition in the regulation of the stress hormone corticosterone (cortisol in humans). Raised levels of circulating corticosterone in germ-free rodents (Crumeyrolle-Arias et al., 2014) are reduced following the administration of probiotics (Sudo et al., 2004), an effect replicated in mice subjected to a stress-inducing behavioural paradigm designed to elevate corticosterone levels (Bravo et al., 2011). However, there is a need for further clarifications of the mechanisms involved in the complex bidirectional relationship between the stress response and the gut microbiota (Bravo et al., 2012; Gareau, Jury, MacQueen, Sherman, & Perdue, 2007).

Most evidence supporting the role of the 'microbiota-gut-brain axis' in humans has come from patients with gastrointestinal disorders (Brenner, Moeller, Chey, & Schoenfeld, 2009; Gareau et al., 2010; Kennedy et al., 2012). Additionally, there is now preliminary evidence for reduced subjective feelings of anxiety and improved aspects of well-being after probiotic intake (Messaoudi et al., 2011; Rao et al., 2009). More recently, a functional MRI investigation found that healthy subjects who received a fermented milk product with probiotics showed decreased BOLD activity to an emotional attention task using facial expressions in the insula and somatosensory regions (Tillisch et al., 2013). These areas play a crucial role in the integration of visceral inputs and the processing of emotional and interoceptive information (Craig, 2009). The study thus convincingly demonstrates that manipulations of the gut microbiota result in measurable changes in emotional processing in the healthy brain.

6.1.2. Emotional attention and perception

As outlined in previous chapters, neural and behavioural biases in the processing of emotional information, in particular increased processing of threat-related and negatively valenced stimuli, are core functional markers of anxiety and depression (Beck, 2008; Cisler & Koster, 2010). These markers are evident in symptomatic patients (Sheline et al., 2001) as well as high-risk (Chan, Goodwin, & Harmer, 2007) and remitted groups (Bhagwagar & Cowen, 2007), and are essential to our understanding of disease symptomatology and treatment efficacy (Elliott, Zahn, Deakin, & Anderson, 2011; Harmer, Goodwin, & Cowen, 2009). Notably, the extent to which these biases can be modulated by pharmacological therapies in patients has been found to be indicative of treatment response (Pizzagalli, 2010; Sheline et al., 2001) and assessing novel compounds on their ability to target emotional biases may thus provide a first line of assessing potential clinical utility.

In addition to the previously discussed enhancements in memory for negative stimuli, prominent features of depressive disorders (and risk thereof) include the interpretation of materials as less positive and more negative (Chan et al., 2007; Hsu, Langenecker, Kennedy, Zubieta, & Heitzeg, 2010; Lee et al., 2007). Individuals with depression have been found to identify ambiguous and neutral stimuli as more negative, to show larger biases towards negative versus positive stimuli, and to preferentially process negative information compared to healthy controls (Kemp & Felmingham, 2008; Kircanski & Gotlib, 2015; Kret & Ploeger, 2015). Stress-related disorders have furthermore been linked with attentional biases, with extensive evidence supporting a close link between biases in the rapid attentional processing of salient negative, particularly threat-related, stimuli and symptoms of anxiety, and evidence for attentional biases particularly at longer stimulus durations in depression (Larson, Nitschke, & Davidson, 2007; Mogg & Bradley, 2005; Peckham, McHugh, & Otto, 2010).

6.1.3. Chapter aims

Given limited evidence of gut microbiota changes on emotional processing and HPA axis activity in humans, a study was performed to test the ability of prebiotic supplements to alter cortisol

reactivity and cognitive-emotional biases in a sample of healthy volunteers. The current chapter presents the results of this study, exploring the effects of two commercially available prebiotics (fructooligosaccharides, [FOS], and Bimuno®-galactooligosaccharides (B-GOS) on the processing of emotional information and HPA axis activity in healthy human volunteers.

6.2. Materials & Methods

6.2.1. Participants & study design

45 volunteers (22 males, 23 females) recruited through online and poster adverts completed the study. Inclusion criteria were: aged 18-45 years; fluent English speaker; BMI range 18-25. Exclusion criteria were: previous or current neurological, psychiatric, gastrointestinal, or endocrine disorders, or other relevant medical history; current or recent (<3 months) regular medication use; previous or current substance/alcohol dependence or abuse within the last three months; regular tobacco use (>5 cigarettes/day); participation in research studies involving medication intake (within 3 months) or prior completion of the Emotional Test Battery (ETB). Participants were assessed with the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997) to confirm the absence of DSM-IV axis-I psychiatric conditions. The study was approved by the Oxford Central University Research Ethics Committee. All participants provided written informed consent and were reimbursed for their time and expenses.

6.2.2. Procedures and tasks

6.2.2.1. Demographic & questionnaire measures

Participants completed the National Adult Reading Test (NART; Nelson, 1982) to provide an estimate of verbal IQ. Self-report questionnaires assessing trait measures of personality (Eysenck Personality Questionnaire, EPQ; Eysenck & Eysenck, 1975), stress responsivity (Perceived Stress Reactivity Scale, PSRS; Schlotz, Yim, Zoccola, Jansen, & Schulz, 2011), subclinical symptoms of depression (Beck Depression Inventory, BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and anxiety (State-Trait Anxiety Inventory, STAI; Spielberger, Gorsuch, & Lushene, 1970) were

also completed. Before and after prebiotic / placebo intake (days 0 and 21, respectively), anxiety (STAI-state), and measures of perceived stress (Perceived Stress Scale, PSS; Cohen, Kamarck, & Mermelstein, 1983) and mood (Visual Analog Scales, VAS, Bond & Lader, 1974; Positive and Negative Affect Schedules, PANAS, Watson, Clark, & Tellegen, 1988) were measured using self-report questionnaires.

6.2.2.2. Prebiotic supplements

The study was placebo-controlled and male/female participants were randomised to receive one of two prebiotics (fructooligosaccharides [N=15; 8 male, 7 female] or Bimuno® - galactooligosaccharides [N=15; 7 male, 8 female]) or a placebo (maltodextrin [N=15; 7 male, 8 female]). Preparations were provided by Clasado Research Services Ltd., Reading, UK. Participants took the supplements (at 5.5g per day) in powder form orally with breakfast for 3 weeks.

6.2.2.3. Salivary cortisol

HPA axis activity was assessed on the day before (Day 0) and on the final day of prebiotic / placebo administration (Day 21), using the salivary cortisol awakening response (CAR; Pruessner et al., 1997). For each CAR measurement, participants were instructed to provide 5 saliva samples (using Salivettes, Sarstedt Ltd., Nümbrecht, Germany) taken in their own home immediately upon waking and subsequently every 15 minutes until 1 hour post-waking. Salivary cortisol was analysed using assay kit l-3002 (Salimetrics Europe Ltd., Newmarket, UK).

6.2.2.4. Emotional processing tasks

On the final day of prebiotic / placebo intake (day 21), participants completed a validated computerised test battery assessing the processing of emotional stimuli (the Emotional Test Battery, ETB; Harmer, Shelley, Cowen, & Goodwin, 2004). The task parameters outlined here for completeness were identical to those described in Chapter 4 (attentional dot probe and facial expression recognition tasks) and Chapter 3 (emotional memory paradigm).

Attentional dot probe task

60 negative and 60 positive words were paired with neutral words matched for length. On each trial, a fixation cross was presented for 500ms in the centre of the screen, followed by two words presented at the top and bottom of the screen. In the unmasked condition, the words were presented for 500ms. In the masked condition, word pairs were presented for 17ms after which a mask was displayed for 483ms. Masks were constructed from digits, letters, and non-letter symbols and were matched for word position and length. Words or masks were replaced by a probe of either one or two stars in the location of one of the preceding stimuli (probes were presented at the top or bottom of the screen with equal frequency). Participants were instructed to indicate the number of stars as quickly and accurately as possible using two labelled keys. A key press terminated the probe presentation and trial. There were 180 trials in total (30 positive-neutral, 30 negative-neutral, 30 neutral-neutral word pairs each for masked and unmasked conditions), and emotional words were presented at the top and the bottom location with equal frequency. Masked and unmasked trials were presented in random order. Reaction time and accuracy scores were recorded, and attentional vigilance scores were calculated for each participant by subtracting the reaction time from trials when probes appeared in the same position as the emotional word (congruent trials) from those trials when probes appeared in the opposite position to the emotional word (incongruent trials).

Facial Expression Recognition Task

In the facial expression recognition task (FERT), the perception of six basic emotions (happiness, surprise, sadness, fear, anger, disgust) or a neutral expression (taken from the Pictures of Affect Series; Ekman & Friesen, 1976) was assessed. Each emotion was shown at 10 morphed intensity levels from neutral to maximum emotional expression (Young et al., 1997) leading to a total of 250 randomly presented stimuli. Each stimulus was presented for 500ms and replaced by a grey screen until the participant responded (as quickly and as accurately as possible) by selecting a key corresponding to one of the basic emotions. The outcome measures were classification accuracy, number of misclassifications, and reaction times.

Emotional categorisation & memory

Sixty words representing either disagreeable (N=30) or agreeable (N=30) personality characteristics (from Anderson, 1968) and matched for meaningfulness, word frequency, and word length were presented on a computer screen for 500ms each. Participants were asked to categorise each word as quickly and accurately as possible according to whether they would like or dislike to be described by it. After completion, participants were instructed to recall and write down as many words as they could within a two-minute time limit. Subsequently, participants were instructed to categorise words presented on the screen into those which were previously presented (60 target words) or those which were novel words 60 matched distracter words). Outcome measures for the emotional categorisation were classifications and reaction times. For the memory recall, the number of correct responses and false positives was recorded, and participants' memory recognition was assessed using correct responses, false positives, and reaction times.

6.2.3. Analysis

Demographic and questionnaire values were analysed using one-way ANOVA with group as factor. Salivary cortisol values (in nMol/l) were square-root transformed and analysed in a mixed design ANOVA with time point of sampling (0, 15, 30, 45, and 60 minutes after waking) and day of sampling (pre- vs. post-treatment) as repeated-measures variables and prebiotic treatment group (Placebo, FOS, or B-GOS) as a between-subjects variable. The behavioural outcome variables of the ETB were also analysed with mixed design ANOVAs, with prebiotic treatment group as between-subjects factor and emotion and task condition as within-subjects factors. Significant interactions were followed up using main effects analyses. Greenhouse-Geisser corrections were used where assumptions of sphericity were not met.

6.3. Results

6.3.1. Demographics & baseline

There were no significant differences between groups for age, trait measures of anxiety, stress reactivity, neuroticism or cognitive status as assessed by digit span (see Table **6-1**). This suggests that groups were well-matched between the two prebiotic and placebo conditions.

Table 6-1. Baseline characteristics of participants in the prebiotics study by treatment group.

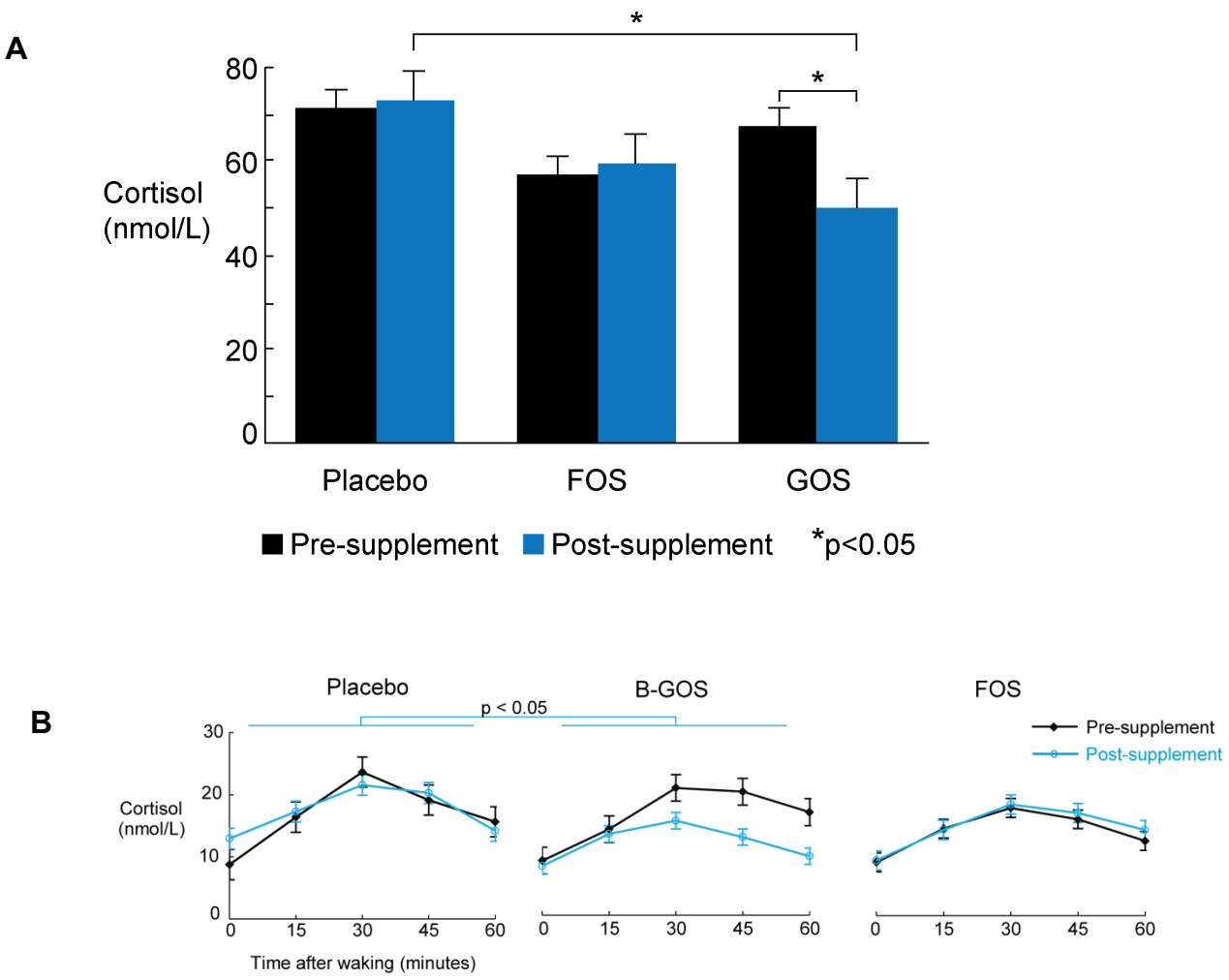
Measure	Placebo	FOS	B-GOS	*p*
Age, in years	23.27 (3.86)	24.53 (3.87)	23.27 (3.95)	*0.31*
NART score	116.50 (5.11)	115.71 (5.24)	112.62 (5.99)	*0.18*
EPQ, Neuroticism	5.17 (4.61)	5.64 (4.22)	4.38 (3.36)	*0.73*
Perceived Stress Reactivity Scale	16.92 (10.06)	16.86 (6.95)	14.38 (5.66)	*0.64*
Beck Depression Inventory	2.58 (4.21)	2.14 (3.04)	2.54 (2.76)	*0.93*
Spielberger Anxiety Inventory, Trait	32.00 (10.33)	32.86 (5.41)	31.69 (4.80)	*0.91*
Digit Span, Forward	10.08 (1.38)	8.43 (2.31)	8.54 (2.60)	*0.12*
Digit Span, Backward	8.50 (1.98)	6.79 (2.52)	7.69 (2.29)	*0.18*

6.3.2. Cortisol

Salivary cortisol did not differ significantly between groups at baseline but was significantly lower following B-GOS compared with placebo (**Figure 6-1**). This was shown by an ANOVA interaction effect of pre- vs. post-treatment, group (placebo, FOS, or B-GOS), and sampling time point (in minutes post-waking) on salivary cortisol levels ($F(3.38, 69.37)=2.01$, $p>0.1$)), followed up with separate group x time-point ANOVAs for each day of sampling (Day 0: main effect of group $F(2,41)=1.08$, $p>0.1$; Day 21: main effect of group $F(2,41)=4.20$, $p<0.02$, followed up with Sidak-corrected contrasts: Placebo vs. GOS $p=0.02$, all others $p>0.1$). Main effects analyses of the day x group x time ANOVA confirmed that cortisol levels were increased post-waking 15, 30, 45, and 60 minutes after waking, (significant main effect of time $F(2.41, 98.63)=58.61$, $p<0.001$, planned follow-up contrasts all significant at $p<0.001$). The main effects of day of sampling and treatment

group were not significant (p>0.1). Gender was not entered as a factor of interest due to insufficient power. The lowered CAR in the B-GOS compared to the placebo group on Day 21 of supplement administration was confirmed when analysing area under the curve with respect to ground (day x group ANOVA on square-root transformed salivary cortisol values: day x group interaction [F(2,41)=3.52, p=0.039], followed up with separate group ANOVAs for pre/Day 0 [F(2,41)=1.24, n.s.] and post/Day 21 [F(2,41)=4.12, p=0.023, follow-up contrasts: Placebo vs. B-GOS p=0.019, Placebo vs. FOS p>0.1, FOS vs B-GOS p>0.1]).

Figure 6-1. Mean cortisol levels (A, area under the curve; B, cortisol awakening response) before and after administration of placebo, B-GOS, or FOS. There were no differences in the salivary CAR at baseline. Salivary cortisol awakening response was significantly lower after 3 weeks B-GOS intake, but not FOS intake, compared with placebo.

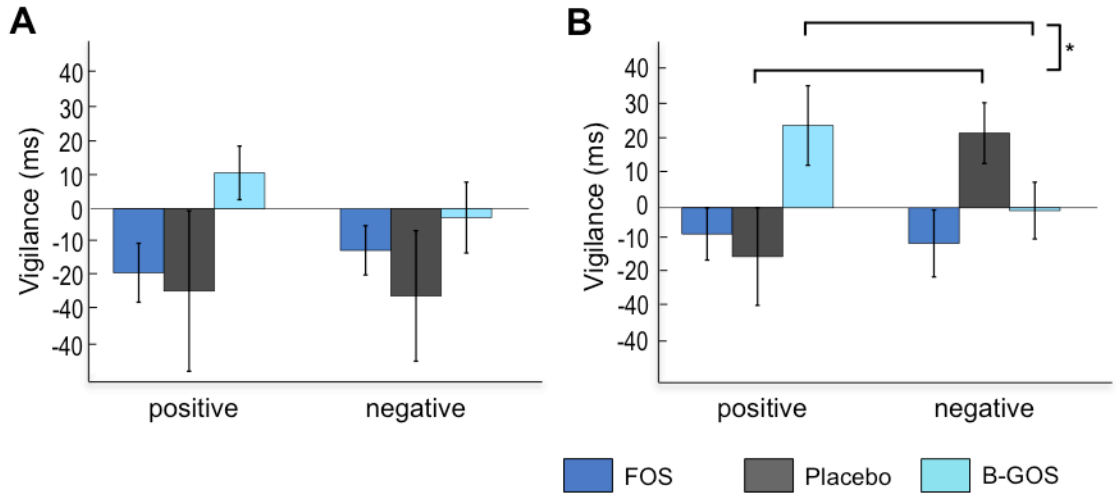


6.3.3. Emotional Test Battery

Attentional dot-probe task

There was a significant group x emotion x masking condition interaction in the visual dot probe task (group x emotion x masking condition [F(2,41)=3.14, p=0.05). As can be seen in **Figure 6-2**, this effect was driven by decreased attentional vigilance to negative versus positive information in the unmasked condition, with no significant main effects or interactions in the masked condition (valence x group interaction in unmasked: F(2,41)=4.29, p=0.02, masked: F(2,41)=0.85, p>0.1). Follow-up analyses with separate ANOVAs for prebiotic group compared with placebo in the unmasked condition confirmed this effect as driven by increased positive versus negative vigilance after B-GOS compared to placebo, while the FOS group did not perform differently to placebo (B-GOS vs. placebo: valence x group F(1,27)=6.94, p=0.014, FOS vs. placebo: valence x group F(1,27)=3.20, *n.s.*).

Figure 6-2. Attentional vigilance (mean ±SEM) in the dot-probe task. A) Attentional vigilance did not differ between groups during masked trials of the attentional dot probe task. B) Participants showed decreased attentional vigilance to negative versus positive words in the unmasked condition of the dot-probe task after Bimuno-galactooligosaccharide® but not fructooligosaccharide intake compared to placebo.



FERT

There were no significant effects of prebiotic treatment on measures of accuracy (main effect of group: F(2,42) = 1.71, *n.s.*, emotion x group interaction F(7.83,164.52)=0.67, *n.s.*). Analysis of

reaction time data revealed no significant interaction between group and emotion (main effect of group: $F(2,42) = 0.53$, *n.s.*, emotion x group interaction $F(8.16,773.38)=1.10$, *n.s.*).

Emotional categorisation, recall, & recognition

Participants responded faster to positive (mean reaction time = 1031ms, SD = 228ms) compared to negative (mean reaction time = 1083ms, SD = 200ms) self-referential personality words in the emotional categoriisation task (valence x group ANOVA, main effect of valence: $F(1,42)=12.82$, $p<0.01$) and in the emotional word recognition task (mean reaction time to positive words=1220.92, SD=263.03; mean reaction time to negative words = 1381.07, SD=348.13; main effect of valence: $F(1,41)=23.34$, $p<0.001$), however, there was no significant main effect of prebiotic treatment group ($F(2,42=0.80$, $p>0.1$) and the relative speeding for positive words did not differ between groups (emotion x group $F(2,42)=0.35$, $p>0.1$). Positive words were also remembered more often than negative words in both the surprise recall task (mean accuracy, positive words = 7.41 (SD=2.45), negative = 5.70 (2.29); $F(1,41)=16.16$, $p<0.001$)) and in the recognition task (mean correct recognition, positive words = 25.67 (SD=3.41), negative words = 22.36 (SD=3.88); $F(1,41)=53.54$, $p<0.001$), but these effect did not differ between groups ($p>0.1$).

6.3.4. Self-report questionnaires

There were no significant effects of group on self-report measures of state anxiety or perceived stress before or after prebiotic / placebo administration (See **Table 6-2**). Furthermore, there were no group differences in the overall cognitive status as assessed by digit span on the day of psychological testing.

Table 6-1-2. State measures of anxiety and perceived stress (mean +/- SD). Ratings before and after prebiotic or placebo administration, and cognitive status on day of assessment (Day 21).

Measure		FOS	Placebo	B-GOS	p
Spielberger Anxiety Inventory, State	Pre (Day 0)	32.00 (7.13)	32.92 (10.03)	32.15 (9.11)	0.96
	Post (Day 21)	30.00 (5.53)	30.17 (7.55)	31.31 (5.23)	0.84
Perceived Stress Scale	Pre (Day 0)	9.86 (4.64)	9.92 (6.05)	10.77 (3.77)	0.87
	Post (Day 21)	9.57 (5.20)	8.92 (5.40)	10.46 (4.86)	0.75
Digit Span (Post, Day 21)	Forward	9.71 (2.40)	10.25 (1.96)	9.54 (2.44)	0.72

Backward	7.50 (2.82)	8.25 (2.73)	8.62 (2.66)	0.56

6.3.5. Correlational analyses

To test the hypothesis that cortisol levels were associated with changes in attentional dot probe performance in the B-GOS group, we correlated difference scores of positive versus negative reaction times in the unmasked condition with absolute cortisol levels upon waking on the day of testing, and with the difference in pre- versus post-prebiotics cortisol values (Day 0 – Day21). There were no associations of cortisol with attentional performance (all $p>0.1$).

6.4. Discussion

6.4.1. Overview

The current study explored the neuroendocrine and affective effects of two types of prebiotic supplements in healthy human volunteers, using salivary CAR and a validated test battery of emotional processing. Results revealed that B-GOS prebiotic intake was associated with decreased waking salivary cortisol reactivity and altered attentional bias compared to placebo. These results are consistent with previously found anxiolytic-like effects of probiotics and reveal key differences between two different prebiotic supplements.

6.4.2. Reduced cortisol following B-GOS

Our findings of lowered cortisol awakening reactivity in the group receiving B-GOS prebiotics compared to the placebo group indicate that prebiotic administration may modulate HPA activity in a similar fashion as the administration of probiotic strains directly seen in rodents (Gareau et al., 2007; Sudo et al., 2004) and humans (Messaoudi et al., 2011). The cortisol awakening response is a reliable marker of HPA axis activity which has been found to be increased by work stressors (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004; Pruessner et al., 1997) and in individuals at high risk of depression (Mannie, Harmer, & Cowen, 2007). Insufficient or excessive cortisol

reactivity may provide useful targets for modulation by alternative treatments in certain vulnerability or disease states (Dinan & Cryan, 2012; Pariante & Lightman, 2008).

6.4.3. Altered attentional vigilance

Participants receiving B-GOS supplements showed increased attentional vigilance to positive versus negative stimuli on the dot-probe task. Our effects are similar to those seen following administration of pharmacological agents such as the selective serotonin reuptake inhibitor citalopram or the benzodiazepine diazepam in healthy individuals (Browning, Reid, Cowen, Goodwin, & Harmer, 2006; S. E. Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009; Susannah E Murphy, Yiend, Lester, Cowen, & Harmer, 2009). These effects have been interpreted as showing an early anxiolytic-like profile, where threatening stimuli are less likely to be attended to (Harmer, 2010). Interestingly, we found effects of the B-GOS prebiotic administration on altered attentional processing only in the unmasked condition (500ms presentation) of the dot probe task. Attentional vigilance to briefly or masked presentations of threatening cues has primarily been interpreted as an involuntary deployment of attention (Browning et al. 2010), whereas at longer stimulus durations it may further involve a difficulty to disengage from salient emotional stimuli (Cisler & Koster, 2010; Koster, Crombez, Verschuere, & De Houwer, 2004). The increase of positive compared to negative emotional information processing in the B-GOS group provides initial evidence that behavioural effects of probiotics in rodent models (Bravo et al., 2011) can be extended to affective processing in humans using prebiotics. These results are also consistent with a recent fMRI study, which reported that 3 week probiotic administration reduced neural response in a network of areas (including the somatosensory cortex, insula and parahippocampal gyrus) to angry and fearful facial expressions (Tillisch et al. 2013).

Differences in attentional resource allocation to negative or positive stimuli are associated with individual variability in trait and state measures. Specifically, vigilance to cues of threat or danger is greater in highly anxious individuals compared with low-anxious individuals and healthy controls (Bradley, Mogg, Falla, & Hamilton, 1998; Koster, Verschuere, Crombez, & Van Damme,

2005; Mogg, Bradley, & Hallowell, 1994), and threat-related processing is believed to play a key role in the symptomatology of anxiety and its modulation by anxiolytics (Beck & Clark, 1997; Bradley et al., 1998). Pharmacological anxiolytics and antidepressants that are clinically effective in reducing symptoms have been found to affect reductions in specific negative biases in neural correlates of emotional information processing (Fu et al., 2004; Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012; Sheline et al., 2001), and also modulate biases when administered in healthy control and at-risk groups (Browning et al., 2006; Harmer et al., 2003; S.E. Murphy et al., 2009). Based on the initial results of gut microbiota interventions, it is now crucial to investigate the extent and specificity of information processing biases that may be targeted by different gut microbiota manipulations and whether they prove clinically beneficial.

6.4.4. Potential mechanisms of action

Although we were unable to test the mechanisms of action directly through characteriisation of gut microbiota, a previous characteriisation of B-GOS and FOS prebiotics showed pronounced increases in *Bifidobacteria* in faecal pellets of rats treated with B-GOS administration compared to placebo, with more moderate effects following the FOS intervention (Savignac et al. 2013). The specificity of galactooligosaccharides affecting behavioural and endocrine changes is thus in line with previous findings of galactooligosaccharides as particularly effective in stimulating enteric microbial growth (Abou Hachem et al., 2013). Of course, the possibility of an additional, direct effect of BGOS on the gut mucosa, cannot be ruled out.

Given the lack of association between altered attentional processes and a reduction in the salivary cortisol awakening response (CAR), we were unable to confirm a moderating effect of cortisol reactivity on behaviour. Although there is strong evidence for a role of the gut microbiota in the regulation of the HPA axis, the exact mechanisms by which they interact with central effects remain to be investigated. One potential mechanism of action underlying these effects is via anti-inflammatory and immune responses following probiotic proliferation (Ait-Belgnaoui et al., 2012;

Lyte, 2011) and central effects of probiotics have been found to be vagus-nerve dependent (Bravo et al. 2011).

6.4.5. Conclusions & Limitations

While initial results of the B-GOS prebiotic on the cortisol awakening response are promising, we had insufficient power to investigate gender effects, which have previously been reported (Pruessner et al. 1997). Further, there were no effects of either prebiotic on the remaining tasks of the ETB which examine aspects of facial expression recognition, self-referential processing and emotional memory. The current results also differ from previous findings that indicate subjective anxiolytic effects of probiotics (Messaoudi et al., 2011; Rao et al., 2009) as we found no effects of prebiotics on subjective measures of subclinical anxiety or perceived stress. One improvement may be to extend the administration period of prebiotics as probiotics take several weeks to proliferate. It is also possible that these results are in part due to our study population of young healthy volunteers with low sub-clinical scores and presumably healthy gut microbiota compositions even before treatment. Studying a population with a potential deficiency in their gut microbiota compositions, for example elderly individuals or patients suffering from irritable bowel syndrome with comorbid psychiatric symptoms, may improve power. The applicability of our results to other populations - such as those with deterioration in the health of their intestinal gut flora or HPA axis abnormalities is a valid next step for future study.

We found a selective modulation of attention to emotional stimuli and HPA axis reactivity following B-GOS prebiotic supplement in healthy participants, supporting a key role for gut microbiota in the regulation of affective function. This, to our knowledge, is the first study extending findings of central effects of probiotics to behavioural effects of prebiotics in humans.

CHAPTER 7: GENERAL DISCUSSION

This chapter presents an overarching discussion of the results from two studies presented within this thesis, which aimed to extend findings of the cognitive-emotional and neural impact of non-acute alterations in HPA axis functioning. Firstly, the main functional – i.e. neural, behavioural, and subjective – findings and how they may be linked are considered, including a discussion of their potential clinical relevance. Finally, the effects of our experimental manipulations on cortisol levels are considered within the context of our wider understanding of glucocorticoid mechanisms, and key methodological considerations, limitations, and future prospects are outlined. Although more research is required to delineate the specificity of these effects, the conclusions drawn from these findings provide further insight into the role of the HPA axis in mechanisms relevant to psychiatric disease.

7.1. Overview of findings

Chapter 2 provided the methodological background for the results of a pharmacological intervention study presented in Chapters 2-5, a 10-day repeated cortisol administration in healthy participants to mimic repeated exposure to stress (*Study 1*). In this well-matched sample of young, healthy volunteers, hydrocortisone administration substantially increased urinary cortisol levels. Additionally, cortisol had particularly strong, but reversible, effects on negative affect and diminished well-being, increasing these compared to placebo at the mid-point of the study. These alterations in negative mood and well-being in response to exogenous cortisol were most strongly apparent in women and within a few days of commencing treatment, which is in line with previous findings of increased prevalence of depression in females, and non-linear (time / dose-specific) responses to glucocorticoid effects on key GR-/MR-dense brain areas.

In Chapter 3, findings of reduced parahippocampal BOLD during a neutral memory task and increased emotional recognition memory of emotional words in participants receiving hydrocortisone provided further support to the extensive evidence base on glucocorticoid

modulation of declarative memory. These effects are consistent with models suggesting stress-induced increases in amygdala-modulated memory and down-regulated hippocampal functioning, although methodological differences to previous tasks necessitate tentative interpretations of potential underlying mechanisms. PFC-dependent working memory was not reliably altered by cortisol, supporting dissociable functional effects of cortisol on different brain regions.

The subsequent chapter from the pharmacological administration study (Chapter 4) extended findings of cortisol's ability to alter the perception of emotional facial expressions, particularly of negative faces. Angry and fearful stimuli were preferentially processed following repeated cortisol, with convincing increases in BOLD in the amygdala and anterior hippocampus, as well as regions in the temporal and occipital lobes. There were no overall effects of hydrocortisone on behavioural measures of emotional processing, although males in the hydrocortisone showed improved recognition of facial emotions compared to males receiving placebo. Further implicit attentional measures showed no effects of cortisol on behaviour.

In the final chapter using data from a repeated cortisol intervention (Chapter 5), validated resting-state connectivity networks were replicated, but these showed no reliable alterations following repeated cortisol. In contrast, seed-to-voxel analyses from the amygdala and hippocampus showed reduced rsFC between these areas and striatal (caudate), occipito-visual, and frontal regions compared to placebo. Additionally, increased rsFC between the amygdala/hippocampus and brainstem areas were found, overlapping with crucial loci of neurotransmitter release.

Chapter 6 presented results from a separate study, in which a strain of prebiotics was found to lower the waking cortisol response in healthy volunteers, and show modest effects on attentional processing of valenced words. This provides further evidence for the ability of gut microbiota to modulate a range of cognitive and emotional functions, although the two effects were not related, suggests that manipulations of HPA axis functioning via the gut microbiota may constitute an intriguing route of research.

7.2. Functional & clinical implications

7.2.1. Altered hippocampal-amygdalar function

In Chapters 3-5, we found that sustained increases in cortisol altered hippocampal function across a number of domains, including neutral and emotional memory, affective processing, and rsFC. Glucocorticoid modulation of hippocampal function appeared to be strongest for emotionally salient materials, implicating the amygdala as a potential mediator of these effects. Hippocampal and amygdalar functions were altered across behavioural (emotional memory), fMRI (neutral memory), and resting-state (rsFC) measures. Furthermore, effects that extended beyond the hippocampus and amygdala to areas of visual, somatosensory, and temporal regions may have been linked to these limbic-temporal areas, highlighting the wide-ranging impact of sustained cortisol changes on cognitive-emotional and neural functioning mediated by the amygdala and hippocampus.

7.2.1.1. Memory

Our results of reduced parahippocampal BOLD during a neutral declarative memory task support and extend previous findings of acute stress interventions and animal studies showing glucocorticoid modulation of hippocampal regions. Specifically, they mimic previous findings of lowered hippocampal activation following sustained increases in cortisol in healthy populations (Brown et al., 2013). Furthermore, reduced parahippocampal activity during encoding of novel stimuli (Chapter 3) has previously been reported in depressed patients using a number of different memory paradigms (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004; Dresler et al., 2011; Fairhall, Sharma, Magnusson, & Murphy, 2010). Although not all studies have replicated this effect (Werner et al., 2009), our findings support accounts of glucocorticoid mechanisms underlying memory alterations that may be related to a dysregulation of hippocampal memory functions in depressive disorders (Abercrombie et al., 2011; Bremner et al., 2004).

Neutral and emotional memory performance were differentially affected by cortisol, with no differences in performance but reduced parahippocampal activation during a neutral memory task,

interpreted as impaired hippocampal memory function, and improved recognition of both positive and negative self-relevant words on an emotional memory paradigm. Our findings are thus in line with a qualitative distinction depending on the salience of stimuli, with neutral declarative memory performance potentially less susceptible/sensitive to the effects of HPA-axis manipulations as emotionally and personally salient emotional memory. These effects are most prominently in agreement with findings of increased amygdala engagement due to emotional stimulus properties altering the functional effects of glucocorticoids on the MTL (Akirav & Richter-Levin, 2006). Given the differences between the neutral (picture) and emotional (self-relevant word) task properties, and the lack of fMRI data from the latter, we were not able to rule out alternative factors in explaining these differences. In particular, we did not include a task containing both neutral and emotional stimuli within the same design for directly comparable results. However, we did include a neutral task with verbal stimuli (the AVLT), which also showed no differences in behavioural performance between the hydrocortisone and placebo groups, supporting stronger modulatory effects of glucocorticoids on emotional memory. Thus, given previous PET and fMRI studies linking parahippocampal activity with successful memory encoding, it is plausible that reduced parahippocampal memory processing following cortisol administration may have been indicative of impaired memory at the neural level, while enhanced amygdalar modulation of the hippocampus may have led to improved recognition memory of emotional words (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Quaedflieg, Schwabe, Meyer, & Smeets, 2013; Schwabe & Wolf, 2012; Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016).

7.2.1.2. Neutral and affective processing

In line with stronger effects of cortisol on emotional compared to neutral memory, BOLD was found to be enhanced, particularly in the anterior hippocampus, during viewing of emotional faces. Findings of increased neural processing of angry and fearful facial expressions support specific effects of cortisol on emotional processing, for example, studies that both endogenous, and acute and repeated administration of glucocorticoids can modulate show enhanced neural processing of negative facial stimuli (Buades-Rotger, Serfling, Harbeck, Brabant, & Krämer, 2016; Carr, Scully,

Webb, & Felmingham, 2016; Feeney, Gaffney, & O'Mara, 2012; Sudheimer et al., 2012). The direction of these effects supports the notion that cortisol increases processing of negative stimuli, yielding biases similar to those associated with depressive symptoms (Ellenbogen, Schwartzman, Stewart, & Walker, 2002; Erickson, Drevets, & Schulkin, 2003). On the other hand, repeated glucocorticoids have previously been associated with reductions in neural activation to negative faces in other brain regions, a discrepancy potentially arising from different task demands.

As in the neutral memory task discussed in Chapter 3, we found that BOLD alterations following hydrocortisone during viewing of faces were localised in the medial temporal lobe. However, these activation differences were in opposite directions, and localised in distinct areas of the hippocampal complex. While the hydrocortisone group showed decreased parahippocampal BOLD during neutral picture learning compared with the placebo group, hydrocortisone was associated with increases in BOLD in the anterior hippocampus during processing of angry and fearful faces. In addition to modulatory effects of the amygdala on the hippocampus under conditions of emotional salience, these differences provide support to recent theories that have attributed distinct functional properties to various hippocampal segments. Specifically, the anterior hippocampus, in conjunction with the amygdala, has been found to underlie the processing and encoding of novel, affectively salient, information (Lisman & Grace, 2005; Murty, Ritchey, Adcock, & LaBar, 2010; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). Our findings thus suggest that glucocorticoids may have the ability to modulate these mechanisms. Specifically, theories of hippocampal affective processing have highlighted its ability to mediate attention and arousal to stimuli requiring a resolution of conflict for action selection and future learning (Bannerman et al., 2014; Buchanan, Tranel, & Kirschbaum, 2009; Chen & Etkin, 2013; Kjelstrup et al., 2002; Poppenk & Moscovitch, 2011). Furthermore, rodent studies implicate the hippocampus in defensive behaviours including freezing, in responding to aversive stimuli in the context of learning, and it is known to be a central regulator of negative HPA axis feedback (Frodl & O'Keane, 2013; Poppenk et al., 2013). Associations between hippocampal structure and function, and both trait and state anxiety in humans (Adhikari, Topiwala, & Gordon, 2010; Rusch, Abercrombie, Oakes, Schaefer, &

Davidson, 2001; Satpute, Mumford, Naliboff, & Poldrack, 2012) further support the notion that altered arousal and behavioural components of anxiety may be related to modulatory hippocampal effects, for example, through the inhibition of active responses to aversive stimuli.

While much research has focussed on the role of fearful stimuli in symptoms of anxiety and depression (Chan, Norbury, Goodwin, & Harmer, 2009; Norbury, Selvaraj, Taylor, Harmer, & Cowen, 2009; Suzuki, Poon, Kumari, & Cleare, 2015), the relevance of anger in clinical development and symptomatology across a range of disorders has increasingly been recognised (Lee et al., 2008; Monk et al., 2006). Altered processing of angry stimuli has been linked to both subclinical trait anxiety (Carre, Fisher, Manuck, & Hariri, 2012; Tran, Lamplmayr, Pintzinger, & Pfabigan, 2013) and clinical anxiety (Monk et al., 2006; Stein, 2002). PTSD, functionally linked to abnormal HPA axis responsivity, has been associated with reduced ERPs to angry faces, potentially indicative of an inability to distinguish between threat and non-threat stimuli (Felmingham, Bryant, & Gordon, 2003). Altered processing of emotional, including angry, faces specifically in the MTL has also been found in patients with schizophrenia, although interpretations remain inconclusive given findings of both increased (Holt et al., 2006) and decreased (Bortolon, Capdevielle, & Raffard, 2015) activation.

Furthermore, increased neural activation in response to angry faces following hydrocortisone is particularly interesting given findings of altered anger processing in the development of psychopathologies in children and adolescents, and the potential role of the HPA axis in developmental trajectories. A recent study found that in adolescents, BOLD activation to angry faces (vs. other emotions) were the only neural predictor of the development of clinical symptoms of anxiety and depression when analysed as a modulator of a genotypic risk profile including CRH variants (Pagliaccio et al., 2015). In line with these findings, Capitao et al. (2014) recently found adolescent depression and first-line antidepressant treatment (for adolescents) to be associated with alterations in biases specifically to angry stimuli. Altered processing of anger during crucial developmental timepoints such as adolescence may thus constitute a relevant and specific indicator of impaired social cue processing indicative of increased likelihood of developing

psychopathologies. Given findings of cortisol as a marker of disease emergence (Lewis, Jones, & Goodyer, 2016), relapse likelihood, and severity (Goodyer, 2015; Herbert, 2012) in those exposed to risk factors, the interaction of cortisol levels and anger processing in the unfolding of interacting risk factors in adolescence may provide a particularly pertinent avenue for further research.

7.2.2. Perceptual, sensory, & salience processing

Enhanced BOLD responses to negative facial expressions following hydrocortisone extended beyond the amygdala and hippocampus into the temporal and temporal fusiform gyri, and somatosensory cortices. The inferior and medial temporal gyri, which constitute part of the ventral visual stream, have consistently been shown to activate preferentially for faces and other stimuli of emotional salience compared to neutral materials (Critchley et al., 2000; Sabatinelli et al., 2014; Sabatini et al., 2009; Satpute et al., 2015), and the increases following hydrocortisone are thus consistent with glucocorticoid-modulated enhancements in rapid perceptual processing of emotionally relevant stimuli. However, while acute stress is thought to rapidly increase attentional vigilance of threatening stimuli, modulation of these areas by a 10-day course of glucocorticoids has, to our knowledge, not previously been shown.

Further increases on early sensory-perceptual processing following sustained hydrocortisone were found in response to the neutral memory task. Participants who received hydrocortisone showed lower activation in the lingual and fusiform gyrus, and occipito-temporal regions, structures previously found to underlie the encoding of visual memory (Leshikar, Duarte, & Hertzog, 2012; Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000). Additionally, hydrocortisone attenuated a decrease in auditory-somatosensory regions (including the superior temporal gyrus and parietal operculum) during encoding (i.e. viewing of novel versus familiar images), which was evident in participants receiving placebo. This decrease in sensory processing of pictorial task stimuli, and decreased suppression of auditory areas may be indicative of reduced specificity of processing or encoding non-affective environmental and task stimuli during the neutral memory task, in line with selective glucocorticoid-modulated increases in emotional processing as discussed

above. Although hypothetical, increases in cortisol may have led to less deactivation associated with task-irrelevant but salient external stimuli (e.g. MRI scanner noise) as well as less specificity in the activation for task-relevant, but neutral visual stimuli.

7.2.3. Altered resting-state connectivity

7.2.3.1. Regions underlying attentional & salience processing

Despite altered neural correlates of facial expression perception and neutral memory, the hydrocortisone and placebo groups showed no differences in previously validated resting state networks, which included temporal, occipital, and attentional regions partially overlapping with regions altered by hydrocortisone during fMRI. However, in agreement with a strong modulatory effect of glucocorticoids on the hippocampus and amygdala, we found widespread alterations in rsFC when these regions were taken into account as seed regions. Pronounced changes in rsFC patterns emerged in areas spanning prelimbic and prefrontal cortices, which showed decreased rsFC with the amygdala/hippocampal seed regions. These areas, particularly the insular cortex, also form part of the salience network and are thought to be involved in the continuous processing and monitoring of biologically salient events in order to direct adaptive behaviours (van Marle, Hermans, Qin, & Fernández, 2010), including homeostatic, interoceptive, and emotional awareness (Seeley et al., 2007; Thomason, Hamilton, & Gotlib, 2011). Acute stress exposure was – contrary to our findings –previously associated with increased rsFC between the amygdala and nodes of the salience network (van Marle ea 2010). It is possible that the repeated pharmacological administration of cortisol in the current results led to an adaptive down-regulation of such mechanisms in healthy participants, associated with decreased resting-state connectivity between these regions. Alternatively, these decreases may relate to reduced interoceptive representations and sensory inputs (Baur, Hänggi, Langer, & Jäncke, 2013), given that in the current study, participants underwent MRI scanning without additional contextual stressors and may have shown enhanced connectivity under conditions of emotional arousal as discussed in relation to the functional tasks.

7.2.3.2. Limbic-temporal connectivity with midbrain regions

Further rsFC decreases were found between the amygdala / hippocampus and localised segments of the striatum, in particular, the head of the caudate. Stressful contexts are known to modulate the extent of striatal engagement during learning and memory (Bennett, 2011; Lingawi & Balleine, 2012; Schwabe & Wolf, 2011), with acute stress usually associated with increased rigid, caudate-based response strategies at the expense of flexible, but cognitively demanding hippocampal-dependent strategies (Kim, Lee, Han, & Packard, 2001; Schwabe, Schächinger, De Kloet, & Oitzl, 2010; Wingard & Packard, 2008). Studies support the involvement of HPA axis alterations beyond acute stress in the regulation of these mechanisms, with young adults exposed to prenatal stress showing increased use of caudate-based versus hippocampal-based learning strategies compared to a non-exposed group (Schwabe et al., 2012). Intriguingly, our findings are in line with studies suggesting stress-related alterations in caudate function and structure, which supports the partial involvement of glucocorticoid factors in disrupted striatal processes. In the highest risk group of a large sample of school-age children (age 9-14, N=120), higher genetic and environmental risk scores (including SNPs within key HPA axis-related genes) were found to predict weaker rsFC between the amygdala and regions including the caudate, inferior and middle frontal gyrus, and parahippocampal gyrus (Pagliaccio et al., 2015). Structural changes in the caudate have been associated with mood changes in Cushing's disease, where increased caudate head (but not the hippocampal) volume was associated with decreases in symptoms of depression and anxiety following treatment (Starkman et al., 2007). Functionally, increased task-based BOLD activation in the head of the caudate has been found in Cushing's Syndrome patients during classification of emotional faces (Langenecker et al., 2012), mirroring findings in depressed patients. These findings are supported by a recent study in which stress-induced anhedonic-like versus resilient mice showed increased measures of diffusion in the caudate, putamen, and amygdala, suggested to reflect striatal reorganiisation after chronic stress (Delgado y Palacios, Verhoye, Henningsen, Wiborg, & Van der Linden, 2014; see also Dias-Ferreira et al., 2009). However, the current pharmacological study did not involve a behavioural paradigm designed to test striatal

mechanisms, and we are therefore unable to associate the resting-state alterations with potential implications for learning and memory.

7.2.4. Potential neurochemical interactions

As outlined in the General Introduction (Chapter 1), cortisol changes associated with HPA axis abnormalities interact bidirectionally with a number of systemic and neurochemical changes to exert functional and behavioural effects. While a full discussion of these interactions is beyond the scope of this thesis, a brief overview of the most relevant provides crucial insight into potential mechanisms underlying the results of our current studies. Although we were unable to test for these effects directly, evidence suggests that arousal associated with encoding emotional stimuli may play a role in emotion- and stress-related improvements in memory at later retrieval (Fastenrath et al., 2014; Schönfeld, Ackermann, & Schwabe, 2014; Steinmetz, Anderson, Brasher, & Brehmer, 2015). In particular, much of the research carried out on glucocorticoid effects on cognition has investigated a link with noradrenergic effects, and suggests that modulation of emotional declarative memory following stress is at least partially mediated by increases in both cortisol and noradrenaline (Hermans et al., 2011; Kukolja, Klingmüller, Maier, Fink, & Hurlemann, 2011; Roozendaal, Okuda, de Quervain, & McGaugh, 2006). It is thus a possibility that the self-evaluative, emotional nature of the verbal encoding and surprise recall tasks induced increased arousal, involving both noradrenergic and glucocorticoid mechanisms. The direction of such mechanisms may differ in patients or at-risk populations – where specific biases towards negative stimuli may be enhanced – compared with the current healthy sample, which showed increased recognition of both positive and negative words. Interestingly, results from resting-state MRI in the current hydrocortisone study showed increased rsFC between the amygdala / hippocampus and an area of the brainstem consistent with the anatomical location of the locus coeruleus, the main locus of noradrenaline release into the CNS (Benarroch, 2009). The locus coeruleus mediates and is mediated by glucocorticoid mechanisms (Curtis, Bello, Connolly, & Valentino, 2002; Jedema, 2004; Valentino, Foote, & Page, 1993; Wang et al., 2015; Zitnik, Curtis, Wood, Arner, & Valentino, 2015), and a potential upregulation of its connectivity with the amygdala / hippocampus

following sustained cortisol is a speculative mechanism that may partially underlie our results. Thus, an interpretation of our results as modulated by glucocorticoids in interaction with noradrenergic effects on the amygdala – which may underlie the emotional memory effects found in Chapter 3, and may be related to altered resting state connectivity as found in Chapter 5 – is supported by strong anatomical and functional links between limbic-temporal with brainstem areas.

7.2.5. Subjective & Clinical

Exactly how the discussed functional alterations may impact subjective well-being remains to be fully elucidated. Nevertheless, our findings are in line with models linking neuropsychological biases as clinically useful markers, and recent extensions have suggested the potential mechanistic links of dysfunctional mood development (Eldar, Rutledge, Dolan, & Niv, 2015; Garrett et al., 2014). Based on these models, abnormalities in the continuous processing of emotional information from our environment underlie many of the symptomatic clinical deficits. In the current thesis, increases in negative affect were found in participants receiving hydrocortisone at the mid-point of the study, but not at the end, when behavioural and fMRI testing took place. Unfortunately, given the limited sample size, we were unable to reliably test for associations between these changes in subjective well-being and behavioural and functional alterations. Nevertheless, subjectively poorer well-being following cortisol administration (Chapter 2) is congruent with the increased processing of negative stimuli in the amygdala and hippocampus (Chapter 4), as increased processing of negative information is thought to be relevant for the maintenance, if not development, of negative mood (Eldar et al., 2015). Previous research supports the ability of glucocorticoids to increase negative affect, and it is important that larger studies are carried out to link these clinically relevant changes with functional cognitive-emotional impairments.

7.3. Methodological considerations

7.3.1. Limitations

Overall, we found that cortisol effects in healthy volunteers were stronger for neural compared to behavioural measures, potentially indicating better sensitivity, and/or compensatory mechanisms in our healthy sample. A strong behavioural effect following repeated hydrocortisone compared with placebo administration was only evident in increased emotional recognition memory (Chapter 3), and for males' increased performance on a facial expression recognition task (Chapter 4). Behavioural responses requiring rapid attentional processing of emotional faces or valenced words did not differ between cortisol and placebo groups, and this lack of strong behavioural effects may be due to either glucocorticoid mechanisms or to methodological limitations. Overall, while our ability to interpret these null effects are limited, it is feasible that cortisol's role in modulating the behavioural correlates of fast attentional processing may be limited, or that insufficient sensitivity of our behavioural measures did not detect effects of cortisol administered at the current dosage, especially in a healthy young population that may be able to employ adaptive mechanisms. The lack of behavioural group differences across the whole sample further validates the usefulness of neural correlates in detecting neurobiological effects of steroids as intermediary measures, particularly in samples of healthy volunteers.

Evidence has long pointed to limbic and temporal regions as a crucial nexus for the effects of glucocorticoids on brain function and stress-related mood and anxiety disorders (Erickson et al., 2003). Despite a plethora of functional and structural MRI findings involving these regions, however, there are methodological difficulties associated with imaging these brain regions. A recent paper highlighted the potential confounding influence of nearby blood vessels on BOLD activation patterns usually associated with functional contrasts of interest (Boubela et al., 2015). An added difficulty is the low spatial resolution and high signal-to-noise ratio within these areas. While discussions regarding the role of the amygdala and hippocampus attempt to dissociate these regions as binary structures, most MRI research conducted on 1.5 or 3T field strengths requires

cautious interpretation of these regions, and is unable to clearly distinguish effects as being clearly hippocampal or amygdalar. Within this thesis, many results are thus discussed with regards to joint functions of these regions, and although this posits a substantial limitation to the current work, methodological advances present an exciting opportunity to address the physiological and functional distinctions between subcomplexes of these ever-relevant structures.

Due to stringent inclusion and exclusion criteria, particularly those concerning own and family history of medical and psychiatric conditions, the repeated-hydrocortisone administration study was concluded before recruitment of the desired number of participants was reached. This led to a lack of statistical power for the analyses carried out in Chapters 2-5, which were nevertheless completed for exploratory purposes, but necessitate caution in the interpretation of the presented results. This is particularly the case for the fMRI analyses reported, the interpretation of which would have benefited considerably from increased power in order to investigate group and gender effects with greater confidence and specificity. Finally, it was not possible to accurately assess menstrual cycle phase for a large proportion of the female sample, due to participants receiving hormonal contraceptives via implants and coil methods. Therefore, menstrual cycle phase was not reported, although it is an evident limitation of the study.

7.3.2. Glucocorticoid mechanisms

Importantly, differences between modulating cortisol acutely (e.g. in agonistic or anticipatory situations) and more chronically appear to confer distinct effects on functional processing, with stable increases in basal levels of cortisol potentially involved in avoidant motivation, and more rapid fluctuations particularly modulating declarative memory and the processing of salient environmental stimuli (e.g. Roelofs, Bakvis, Hermans, van Pelt, & van Honk, 2007). Differences in glucocorticoid kinetics and their slow versus fast-acting physiological effects have further been shown to exert opposing effects in other settings (Henckens, van Wingen, Joëls, & Fernández, 2012). Findings in a range of domains of cognitive and emotional processing support the ability of glucocorticoid manipulations to have either detrimental or beneficial effects on performance

depending on dose and timecourse (Gagnon & Wagner, 2016; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Wolf et al., 2016; Young, Drevets, Schulkin, & Erickson, 2011). These variations may largely be due to differences in glucocorticoid receptor binding based on the dose and timecourse of manipulations (De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998), and variability in the sensitivity to cortisol which may be affected by both individual trait and state differences.

7.4. Conclusion

This thesis presented the findings of two studies, which altered cortisol levels non-acutely. HPA axis manipulations exerted effects on emotional memory, neural correlates of neutral memory and emotional information processing, and resting-state connectivity. Following 10-day of hydrocortisone administration, healthy participants showed reduced parahippocampal BOLD during a neutral memory task and increased emotional recognition memory of emotional words, extending extensive findings of cortisol modulating declarative memory processes. We found no alterations in working memory performance, supporting dissociable functional effects of cortisol on different brain regions. Furthermore, neural temporo-limbic correlates of negative, particularly angry, facial expression perception were increased by cortisol, although we failed to find a clear link with behavioural performance, which may be less sensitive. More implicit attentional measures also show no effect of cortisol on behaviour. The GR-/MR-mediated neural structures underlying hydrocortisone-induced alterations in memory and emotional processing have been extensively studied in animals and – increasingly – in humans. Overall, these previous and our current findings suggest that increases in amygdalar-hippocampal function due to HPA axis alterations may have driven these effects. Although some methodological shortcomings require cautious mechanistic interpretations, these findings provide novel evidence of non-acute cortisol increases modulating biases in a wide range of behavioural domains and neural functional and resting-state circuitries associated with abnormal emotional salience processing, declarative memory, and reward learning in psychiatric disorders. The results suggest that repeated cortisol increases may be particularly relevant to memory impairments and social threat perception and their neural correlates in the hippocampus/amygdala, and neural connectivity alterations at rest that may be relevant for

affective learning mechanisms and homeostatic salience. In contrast, reliable behavioural alterations in attentional biases were not evident after sustained increases in cortisol. Finally, a separate study provided initial confirmation that alterations in gut microbiota via 3-week ingestion of a prebiotic may have the ability to alter HPA axis functioning in healthy humans, and was further associated with increased positive versus negative attentional vigilance. Wider interactions of the HPA axis are increasingly being specified, and may allow the development of novel (indirect) therapeutic targets.

REFERENCES

Aardal-Eriksson, E., Eriksson, T. E., & Thorell, L.-H. (2001). Salivary cortisol, posttraumatic stress symptoms, and general health in the acute phase and during 9-month follow-up. *Biological Psychiatry*, *50*(12), 986–993. https://doi.org/10.1016/S0006-3223(01)01253-7

Aas, M., Dazzan, P., Mondelli, V., Toulopoulou, T., Reichenberg, A., Forti, M. D., … Pariante, C. M. (2011). Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychological Medicine*, *41*(3), 463–476. https://doi.org/10.1017/S0033291710001170

Abercrombie, H. C., Jahn, A. L., Davidson, R. J., Kern, S., Kirschbaum, C., & Halverson, J. (2011). Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. *Journal of Psychiatric Research*, *45*(1), 15–23. https://doi.org/10.1016/j.jpsychires.2010.10.005

Abercrombie, H. C., Speck, N., & Monticelli, R. (2006). Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. *Psychoneuroendocrinology*, *31*(2), 187–196. https://doi.org/10.1016/j.psyneuen.2005.06.008

Abercrombie, H. C., Wirth, M. M., & Hoks, R. M. (2012). Inter-individual differences in trait negative affect moderate cortisol's effects on memory formation: Preliminary findings from two studies. *Psychoneuroendocrinology*, *37*(5), 693–701. https://doi.org/10.1016/j.psyneuen.2011.08.014

Abou Hachem, M., Andersen, J. M., Barrangou, R., Møller, M. S., Fredslund, F., Majumder, A., … Svensson, B. (2013). Recent insight into oligosaccharide uptake and metabolism in probiotic bacteria. *Biocatalysis and Biotransformation*, *31*(4), 226–235. https://doi.org/10.3109/10242422.2013.828048

Adam, E. K., Doane, L. D., Zinbarg, R. E., Mineka, S., Craske, M. G., & Griffith, J. W. (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. *Psychoneuroendocrinology*, *35*(6), 921–931. https://doi.org/10.1016/j.psyneuen.2009.12.007

Adhikari, A., Topiwala, M. A., & Gordon, J. A. (2010). Synchronized Activity between the Ventral Hippocampus and the Medial Prefrontal Cortex during Anxiety. *Neuron*, *65*(2), 257–269. https://doi.org/10.1016/j.neuron.2009.12.002

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory*, *4*(3), 291–300. https://doi.org/10.1101/lm.4.3.291

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., … Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, *37*(10), 1111–1117. Retrieved from http://www.sciencedirect.com/science/article/pii/S0028393299000391

Ahdidan, J., Hviid, L. B., Chakravarty, M. M., Ravnkilde, B., Rosenberg, R., Rodell, A., … Videbech, P. (2011). Longitudinal MR study of brain structure and hippocampus volume in major depressive disorder. *Acta Psychiatrica Scandinavica*, *123*(3), 211–219. https://doi.org/10.1111/j.1600-0447.2010.01644.x

Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., … Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, *37*(11), 1885–1895. https://doi.org/10.1016/j.psyneuen.2012.03.024

Akirav, I., & Richter-Levin, G. (2002). Mechanisms of amygdala modulation of hippocampal plasticity. *The Journal of Neuroscience*, *22*(22), 9912–9921. Retrieved from http://www.jneurosci.org/content/22/22/9912.short

Akirav, I., & Richter-Levin, G. (2006). Factors that Determine the Non-Linear Amygdala Influence on Hippocampus-Dependent Memory. *Dose-Response*, *4*(1), 22–37. https://doi.org/10.2203/dose-response.004.01.003.Akirav

Alexander, N., Kuepper, Y., Schmitz, A., Osinsky, R., Kozyra, E., & Hennig, J. (2009). Gene–environment interactions predict cortisol responses after acute stress: Implications for the etiology of depression. *Psychoneuroendocrinology*, *34*(9), 1294–1303. https://doi.org/10.1016/j.psyneuen.2009.03.017

Alkire, M. T., Haier, R. J., Fallon, J. H., & Cahill, L. (1998). Hippocampal, but not amygdala, activity at encoding correlates with long-term, free recall of nonemotional information. *Proceedings of the National Academy of Sciences*, *95*(24), 14506–14510. Retrieved from http://www.pnas.org/content/95/24/14506.short

Allen MG. (1976). TWin studies of affective illness. *Archives of General Psychiatry*, *33*(12), 1476–1478. https://doi.org/10.1001/archpsyc.1976.01770120080008

Almeida, I., van Asselen, M., & Castelo-Branco, M. (2013). The role of the amygdala and the basal ganglia in visual processing of central vs. peripheral emotional content. *Neuropsychologia*, *51*(11), 2120–2129. https://doi.org/10.1016/j.neuropsychologia.2013.07.007

Amico, F., Meisenzahl, E., Koutsouleris, N., Reiser, M., Möller, H.-J., & Frodl, T. (2011). Structural MRI correlates for vulnerability and resilience to major depressive disorder. *Journal of Psychiatry & Neuroscience : JPN*, *36*(1), 15–22. https://doi.org/10.1503/jpn.090186

Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P. A., Milanesi, E., … Thuret, S. (2012). Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. *Neuropsychopharmacology*, *38*(5), 872–883. Retrieved from http://www.nature.com/npp/journal/v38/n5/abs/npp2012253a.html

Anacker, C., O'Donnell, K. J., & Meaney, M. J. (2014). Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. *Dialogues in Clinical Neuroscience*, *16*(3), 321. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214175/

Anacker, C., & Pariante, C. M. (2012). New models to investigate complex glucocorticoid receptor functions. *Frontiers in Behavioral Neuroscience*, *6*. https://doi.org/10.3389/fnbeh.2012.00090

Anacker, C., Zunszain, P. A., Carvalho, L. A., & Pariante, C. M. (2011). The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology*, *36*(3), 415–425. https://doi.org/10.1016/j.psyneuen.2010.03.007

Anand, A., Li, Y., Wang, Y., Lowe, M. J., & Dzemidzic, M. (2009). Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research: Neuroimaging*, *171*(3), 189–198. https://doi.org/10.1016/j.pscychresns.2008.03.012

Andela, C. D., Haalen, F. M. van, Ragnarsson, O., Papakokkinou, E., Johannsson, G., Santos, A., … Pereira, A. M. (2015). MECHANISMS IN ENDOCRINOLOGY: Cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies. *European Journal of Endocrinology*, *173*(1), R1–R14. https://doi.org/10.1530/EJE-14-1101

Anderson, N. (1968). Likableness ratings of 555 personality trait words. *Journal of Personality and Social Psychology*, *9*, 272–279.

Andersson, J. L., Jenkinson, M., Smith, S., & Andersson, J. (2007). *Non-linear registration aka Spatial normalisation FMRIB Technial Report TR07JA2*. (No. TR07JA2). Retrieved from http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT

Anticevic, A., Hu, S., Zhang, S., Savic, A., Billingslea, E., Wasylink, S., … Pittenger, C. (2014). Global resting-state fMRI analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biological Psychiatry*, *75*(8), 595–605. https://doi.org/10.1016/j.biopsych.2013.10.021

Arguello, P. A., & Gogos, J. A. (2012). Genetic and cognitive windows into circuit mechanisms of psychiatric disease. *Trends in Neurosciences*, *35*(1), 3–13. https://doi.org/10.1016/j.tins.2011.11.007

Armony, J. L. (2013). Current Emotion Research in Behavioral Neuroscience: The Role(s) of the Amygdala. *Emotion Review*, *5*(1), 104–115.

Arnone, D., McIntosh, A. M., Ebmeier, K. P., Munafò, M. R., & Anderson, I. M. (2012). Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. *European Neuropsychopharmacology*, *22*(1), 1–16. https://doi.org/10.1016/j.euroneuro.2011.05.003

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Arnsten, A. F. T. (2015). Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature Neuroscience*, *18*(10), 1376–1385. https://doi.org/10.1038/nn.4087

Arnsten, A. F. T., & Jin, L. E. (2014). Molecular Influences on Working Memory Circuits in Dorsolateral Prefrontal Cortex. In *Progress in Molecular Biology and Translational Science* (Vol. 122, pp. 211–231). Elsevier. Retrieved from http://linkinghub.elsevier.com/retrieve/pii/B9780124201705000088

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences*, *18*(4), 177–185. https://doi.org/10.1016/j.tics.2013.12.003

Bach, D. R., Guitart-Masip, M., Packard, P. A., Miró, J., Falip, M., Fuentemilla, L., & Dolan, R. J. (2014). Human Hippocampus Arbitrates Approach-Avoidance Conflict. *Current Biology*, *24*(5), 541–547. https://doi.org/10.1016/j.cub.2014.01.046

Bangasser, D. A., & Kawasumi, Y. (2015). Cognitive disruptions in stress-related psychiatric disorders: A role for corticotropin releasing factor (CRF). *Hormones and Behavior*, *76*, 125–135. https://doi.org/10.1016/j.yhbeh.2015.04.003

Bannerman, D. M., Grubb, M., Deacon, R. M. J., Yee, B. K., Feldon, J., & Rawlins, J. N. P. (2003). Ventral hippocampal lesions affect anxiety but not spatial learning. *Behavioural Brain Research*, *139*(1), 197–213. Retrieved from http://www.sciencedirect.com/science/article/pii/S0166432802002681

Bannerman, D. M., Rawlins, J. N. P., McHugh, S. B., Deacon, R. M. J., Yee, B. K., Bast, T., … Feldon, J. (2004). Regional dissociations within the hippocampus—memory and anxiety. *Neuroscience & Biobehavioral Reviews*, *28*(3), 273–283. https://doi.org/10.1016/j.neubiorev.2004.03.004

Bannerman, D. M., Sprengel, R., Sanderson, D. J., McHugh, S. B., Rawlins, J. N. P., Monyer, H., & Seeburg, P. H. (2014). Hippocampal synaptic plasticity, spatial memory and anxiety. *Nature Reviews Neuroscience*, *15*(3), 181–192. Retrieved from http://www.nature.com/nrn/journal/v15/n3/abs/nrn3677.html

Bannerman, D. M., Yee, B. K., Good, M. A., Heupel, M. J., Iversen, S. D., & Rawlins, J. N. P. (1999). Double dissociation of function within the hippocampus: A comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions. *Behavioral Neuroscience*, *113*(6), 1170–1188. https://doi.org/10.1037/0735-7044.113.6.1170

Barense, M. D. (2005). Functional Specialization in the Human Medial Temporal Lobe. *Journal of Neuroscience*, *25*(44), 10239–10246. https://doi.org/10.1523/JNEUROSCI.2704-05.2005

Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, *45*(13), 2963–2974. https://doi.org/10.1016/j.neuropsychologia.2007.05.023

Barnhofer, T., Kuehn, E.-M., & de Jong-Meyer, R. (2005). Specificity of autobiographical memories and basal cortisol levels in patients with major depression. *Psychoneuroendocrinology*, *30*(4), 403–411. https://doi.org/10.1016/j.psyneuen.2004.11.005

Barrett, L. F., Lindquist, K. A., Bliss-Moreau, E., Duncan, S., Gendron, M., Mize, J., & Brennan, L. (2007). Of Mice and Men: Natural Kinds of Emotions in the Mammalian Brain? A Response to Panksepp and Izard. *Perspectives on Psychological Science*, *2*(3), 297–312. https://doi.org/10.1111/j.1745-6916.2007.00046.x

Barry, T. J., Murray, L., Fearon, R. M. P., Moutsiana, C., Cooper, P., Goodyer, I. M., … Halligan, S. L. (2015). Maternal postnatal depression predicts altered offspring biological stress reactivity in adulthood. *Psychoneuroendocrinology*, *52*, 251–260. https://doi.org/10.1016/j.psyneuen.2014.12.003

Bartolomucci, A., Carola, V., Pascucci, T., Puglisi-Allegra, S., Cabib, S., Lesch, K.-P., … Gross, C. (2010). Increased vulnerability to psychosocial stress in heterozygous serotonin transporter knockout mice. *Disease Models & Mechanisms*, *3*(7–8), 459–470. https://doi.org/10.1242/dmm.004614

Bartsch, T. (Ed.). (2012). *The Clinical Neurobiology of the Hippocampus: An integrative view*. Oxford University Press. Retrieved from http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780199592388.001.0001/acprof-9780199592388

Baumeister, D., Lightman, S. L., & Pariante, C. M. (2014). The interface of stress and the HPA axis in behavioural phenotypes of mental illness. In *Current Topics in Behavioral Neurosciences* (Vol. 18, pp. 13–24).

Baumeister, H., & Parker, G. (2012). Meta-review of depressive subtyping models. *Journal of Affective Disorders*, *139*(2), 126–140. https://doi.org/10.1016/j.jad.2011.07.015

Baur, V., Hänggi, J., Langer, N., & Jäncke, L. (2013). Resting-State Functional and Structural Connectivity Within an Insula–Amygdala Route Specifically Index State and Trait Anxiety. *Biological Psychiatry*, *73*(1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003

Bebko, G., Bertocci, M., Chase, H., Dwojak, A., Bonar, L., Almeida, J., … Phillips, M. L. (2015). Decreased amygdala–insula resting state connectivity in behaviorally and emotionally dysregulated youth. *Psychiatry Research: Neuroimaging*, *231*(1), 77–86. https://doi.org/10.1016/j.pscychresns.2014.10.015

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry*, *165*(8), 969–977. Retrieved from http://journals.psychiatryonline.org/article.aspx?articleid=100047

Beck, A. T., & Clark, D. A. (1997). An information processing model of anxiety: automatic and strategic processes. *Behaviour Research and Therapy*, *35*(1), 49–58.

Beck, A. T., Ward, C., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571.

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *360*(1457), 1001–1013. https://doi.org/10.1098/rstb.2005.1634

Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, *23*(2), 137–152. https://doi.org/10.1109/TMI.2003.822821

Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. *NeuroImage*, *47*, S148. https://doi.org/10.1016/S1053-8119(09)71511-3

Belanoff, J. K., Kalehzan, M., Sund, B., Ficek, S. K. F., & Schatzberg, A. F. (2014). Cortisol activity and cognitive changes in psychotic major depression. Retrieved from http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.158.10.1612

Bellavance, M.-A., & Rivest, S. (2014). The HPA & Immune Axis and the Immunomodulatory Actions of Glucocorticoids in the Brain. *Frontiers in Immunology*, *5*. https://doi.org/10.3389/fimmu.2014.00136

Belvederi, M., Prestia, D., Mondelli, V., Pariante, C. M., Patti, S., Olivieri, B., … Amore, M. (2016). The HPA axis in bipolar disorder: Systematic review and meta-analysis. *Psychoneuroendocrinology*, *63*, 327–342. https://doi.org/10.1016/j.psyneuen.2015.10.014

Belvederi Murri, M., Pariante, C. M., Mondelli, V., Masotti, M., Atti, A. R., Mellacqua, Z., … Amore, M. (2014). HPA axis and aging in depression: Systematic review and meta-analysis. *Psychoneuroendocrinology*, *41*, 46–62. https://doi.org/10.1016/j.psyneuen.2013.12.004

Benarroch, E. E. (2009). The locus ceruleus norepinephrine system Functional organization and potential clinical significance. *Neurology*.

Bennett, M. R. (2011). The prefrontal–limbic network in depression: Modulation by hypothalamus, basal ganglia and midbrain. *Progress in Neurobiology*, *93*(4), 468–487. https://doi.org/10.1016/j.pneurobio.2011.01.006

Berridge, C. W. (2009). The Locus Coeruleus-Noradrenergic System and Stress: Implications for Post-Traumatic Stress Disorder. In J. E. LeDoux, T. Keane, & P. Shiromani (Eds.), *Post-Traumatic Stress Disorder* (pp. 213–230). Humana Press. https://doi.org/10.1007/978-1-60327-329-9_10

Bertsch, K., Böhnke, R., Kruk, M. R., Richter, S., & Naumann, E. (2011). Exogenous cortisol facilitates responses to social threat under high provocation. *Hormones and Behavior*, *59*(4), 428–434. https://doi.org/10.1016/j.yhbeh.2010.12.010

Bhagwagar, Z., & Cowen, P. J. (2007). 'It's not over when it's over': persistent neurobiological abnormalities in recovered depressed patients. *Psychological Medicine*, *38*(3). https://doi.org/10.1017/S0033291707001250

Bhagwagar, Z., Hafizi, S., & Cowen, P. J. (2005). Increased salivary cortisol after waking in depression. *Psychopharmacology*, *182*(1), 54–57. https://doi.org/10.1007/s00213-005-0062-z

Bick, J., & Nelson, C. A. (2016). Early Adverse Experiences and the Developing Brain. *Neuropsychopharmacology*, *41*(1), 177–196. https://doi.org/10.1038/npp.2015.252

Bingel, U., Rose, M., Gläscher, J., & Büchel, C. (2007). fMRI Reveals How Pain Modulates Visual Object Processing in the Ventral Visual Stream. *Neuron*, *55*(1), 157–167. https://doi.org/10.1016/j.neuron.2007.05.032

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Bogdan, R., Pagliaccio, D., Baranger, D. A., & Hariri, A. R. (2016). Genetic moderation of stress effects on corticolimbic circuitry. *Neuropsychopharmacology*, *41*(1), 275–296. Retrieved from http://www.nature.com/npp/journal/v41/n1/abs/npp2015216a.html

Böhnke, R., Bertsch, K., Kruk, M. R., Richter, S., & Naumann, E. (2010). Exogenous cortisol enhances aggressive behavior in females, but not in males. *Psychoneuroendocrinology*, *35*(7), 1034–1044. https://doi.org/10.1016/j.psyneuen.2010.01.004

Bolanos, S. H., Khan, D. A., Hanczyc, M., Bauer, M. S., Dhanani, N., & Brown, E. S. (2004). Assessment of mood states in patients receiving long-term corticosteroid therapy and in controls with patient-rated and clinician-rated scales. *Annals of Allergy, Asthma & Immunology*, *92*, 500–505.

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*, *47*, 211–218.

Bonner, M. F., Price, A. R., Peelle, J. E., & Grossman, M. (2015). Semantics of the Visual Environment Encoded in Parahippocampal Cortex. *Journal of Cognitive Neuroscience*, 1–18. https://doi.org/10.1162/jocn_a_00908

Bortolon, C., Capdevielle, D., & Raffard, S. (2015). Face recognition in schizophrenia disorder: A comprehensive review of behavioral, neuroimaging and neurophysiological studies. *Neuroscience & Biobehavioral Reviews*, *53*, 79–107. https://doi.org/10.1016/j.neubiorev.2015.03.006

Boubela, R. N., Kalcher, K., Huf, W., Seidel, E.-M., Derntl, B., Pezawas, L., … Moser, E. (2015). fMRI measurements of amygdala activation are confounded by stimulus correlated signal fluctuation in nearby veins draining distant brain regions. *Scientific Reports*, *5*, 10499. https://doi.org/10.1038/srep10499

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in major depression: a review. *Australian and New Zealand Journal of Psychiatry*, *44*(8), 681–696. Retrieved from http://www.tandfonline.com/doi/abs/10.3109/00048674.2010.496359

Bowers, M. E., & Yehuda, R. (2016). Intergenerational Transmission of Stress in Humans. *Neuropsychopharmacology*, *41*(1), 232–244. https://doi.org/10.1038/npp.2015.247

Bradley, B. P., Mogg, K., Falla, S. J., & Hamilton, L. R. (1998). Attentional Bias for Threatening Facial Expressions in Anxiety: Manipulation of Stimulus Duration. *Cognition & Emotion*, *12*(6), 737–753. https://doi.org/10.1080/026999398379411

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., … Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, *108*(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

Bravo, J. A., Julio-Pieper, M., Forsythe, P., Kunze, W., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2012). Communication between gastrointestinal bacteria and the nervous system. *Current Opinion in Pharmacology*, 1–6. https://doi.org/10.1016/j.coph.2012.09.010

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., … Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, *17*(5), 875–887. Retrieved from http://www.sciencedirect.com/science/article/pii/S0896627300802196

Bremner, J. D., Vythilingam, M., Vermetten, E., Vaccarino, V., & Charney, D. S. (2004). Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *American Journal of Psychiatry*, *161*(4), 637–645. Retrieved from http://journals.psychiatryonline.org/article.aspx?articleid=176730

Brenner, D. M., Moeller, M. J., Chey, W. D., & Schoenfeld, P. S. (2009). The Utility of Probiotics in the Treatment of Irritable Bowel Syndrome: A Systematic Review. *American Journal of Gastroenterology*, *104*, 1033–1049.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Making Memories: Brain Activity that Predicts How Well Visual Experience Will Be Remembered. *Science*, *281*(5380), 1185–1187. https://doi.org/10.1126/science.281.5380.1185

Britton, J. C., Taylor, S. F., Sudheimer, K. D., & Liberzon, I. (2006). Facial expressions and complex IAPS pictures: Common and differential networks. *NeuroImage*, *31*(2), 906–919. https://doi.org/10.1016/j.neuroimage.2005.12.050

Brodbeck, J., Goodyer, I. M., Abbott, R. A., Dunn, V. J., St Clair, M. C., Owens, M., … Croudace, T. J. (2014). General distress, hopelessness—suicidal ideation and worrying in adolescence: Concurrent and predictive validity of a symptom-level bifactor model for clinical diagnoses. *Journal of Affective Disorders*, *152–154*, 299–305. https://doi.org/10.1016/j.jad.2013.09.029

Brown, E. S. (2009). Effects of Glucocorticoids on Mood, Memory, and the Hippocampus: Treatment and Preventive Therapy. *Annals of the New York Academy of Sciences*, *1179*(1), 41–55. https://doi.org/10.1111/j.1749-6632.2009.04981.x

Brown, E. S., Beard, L., Frol, A. B., & Rush, A. J. (2006). Effect of two prednisone exposures on mood and declarative memory. *Neurobiology of Learning and Memory*, *86*(1), 28–34. https://doi.org/10.1016/j.nlm.2005.12.009

Brown, E. S., & Chandler, P. A. (2001). Mood and Cognitive Changes During Systemic Corticosteroid Therapy. *The Primary Care Companion to the Journal of Clinical Psychiatry*, *3*, 17–21.

Brown, E. S., J. Woolston, D., Frol, A., Bobadilla, L., Khan, D. A., Hanczyc, M., … Cullum, C. M. (2004). Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biological Psychiatry*, *55*(5), 538–545. https://doi.org/10.1016/j.biopsych.2003.09.010

Brown, E. S., Jeon-Slaughter, H., Lu, H., Jamadar, R., Issac, S., Shad, M., … Thomas, B. P. (2015). Hippocampal Volume in Healthy Controls Given 3-Day Stress Doses of Hydrocortisone. *Neuropsychopharmacology*, *40*, 1216–1221. https://doi.org/10.1038/npp.2014.307

Brown, E. S., Lu, H., Denniston, D., Uh, J., Thomas, B. P., Carmody, T. J., … Tamminga, C. (2013). A randomized, placebo-controlled proof-of-concept, crossover trial of phenytoin for hydrocortisone-induced declarative memory changes. *Journal of Affective Disorders*, *150*(2), 551–558. https://doi.org/10.1016/j.jad.2013.01.038

Brown, E. S., Rush, a J., & McEwen, B. S. (1999). Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *21*(4), 474–84. https://doi.org/10.1016/S0893-133X(99)00054-8

Brown, E. S., Suppes, T., Khan, D. A., & Carmody, T. J. (2002). Mood changes during prednisone bursts in outpatients with asthma. *Journal of Clinical Psychopharmacology*, *22*(1), 55–61. Retrieved from http://journals.lww.com/psychopharmacology/Abstract/2002/02000/Mood_Changes_During_Prednisone_Bursts_in.9.aspx

Brown, E. S., Vera, E., Frol, A. B., Woolston, D. J., & Johnson, B. (2007). Effects of chronic prednisone therapy on mood and memory. *Journal of Affective Disorders*, *99*(1–3), 279–283. https://doi.org/10.1016/j.jad.2006.09.004

Brown, E. S., Woolston, D. J., & Frol, A. B. (2008). Amygdala Volume in Patients Receiving Chronic Corticosteroid Therapy. *Biological Psychiatry*, *63*(7), 705–709. https://doi.org/10.1016/j.biopsych.2007.09.014

Browning, M., Reid, C., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2006). A single dose of citalopram increases fear recognition in healthy subjects. *Journal of Psychopharmacology*, *21*(7), 684–690. https://doi.org/10.1177/0269881106074062

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009a). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, *33*(3), 279–296. https://doi.org/10.1016/j.neubiorev.2008.09.002

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009b). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, *33*(3), 279–296. https://doi.org/10.1016/j.neubiorev.2008.09.002

Buades-Rotger, M., Serfling, G., Harbeck, B., Brabant, G., & Krämer, U. M. (2016). Prednisolone increases neural reactivity to negative socio-emotional stimuli in healthy young men. *European Neuropsychopharmacology*. https://doi.org/10.1016/j.euroneuro.2016.04.010

Buchanan, T. W., Kern, S., Allen, J. S., Tranel, D., & Kirschbaum, C. (2004). Circadian regulation of cortisol after hippocampal damage in humans. *Biological Psychiatry*, *56*(9), 651–656. https://doi.org/10.1016/j.biopsych.2004.08.014

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology*, *26*(3), 307–317. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453000000585

Buchanan, T. W., Tranel, D., & Kirschbaum, C. (2009). Hippocampal damage abolishes the cortisol response to psychosocial stress in humans. *Hormones and Behavior*, *56*(1), 44–50. https://doi.org/10.1016/j.yhbeh.2009.02.011

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, *30*(9), 846–856. https://doi.org/10.1016/j.psyneuen.2005.02.010

Cabeza, R., & Nyberg, L. (2000). Imaging Cognition II: An Empirical Review of 275 PET and fMRI Studies. *Journal of Cognitive Neuroscience*, *12*(1), 1–47. https://doi.org/10.1162/08989290051137585

Calder, A. J., & Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews Neuroscience*, *6*(8), 641–651. https://doi.org/10.1038/nrn1724

Campbell, S., & Macqueen, G. (2004). The role of the hippocampus in the pathophysiology of major depression. *Journal of Psychiatry & Neuroscience*, *29*(6), 417–426. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=16304851

Capitao, L. (2014). *Early effects of fluoxetine on emotional processing: implications for adolescent depression*. University of Oxford, Oxford, UK.

Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, *26*(3), 321–352. Retrieved from http://www.sciencedirect.com/science/article/pii/S0149763402000076

Carlson, J. M., Depetro, E., Maxwell, J., Harmon-Jones, E., & Hajcak, G. (2015). Gender moderates the association between dorsal medial prefrontal cortex volume and depressive symptoms in a subclinical sample. *Psychiatry Research: Neuroimaging*, *233*(2), 285–288. https://doi.org/10.1016/j.pscychresns.2015.06.005

Carnegie, R., Araya, R., Ben-Shlomo, Y., Glover, V., O'Connor, T. G., O'Donnell, K. J., … Lewis, G. (2014). Cortisol awakening response and subsequent depression: prospective longitudinal study. *The British Journal of Psychiatry*, *204*(2), 137–143. https://doi.org/10.1192/bjp.bp.113.126250

Carpenter, L. L., Ross, N. S., Tyrka, A. R., Anderson, G. M., Kelly, M., & Price, L. H. (2009). Dex/CRH test cortisol response in outpatients with major depression and matched healthy controls. *Psychoneuroendocrinology*, *34*(8), 1208–1213. https://doi.org/10.1016/j.psyneuen.2009.03.009

Carr, A. R., Scully, A., Webb, M., & Felmingham, K. L. (2016). Gender differences in salivary alpha-amylase and attentional bias towards negative facial expressions following acute stress induction. *Cognition and Emotion*, *30*(2), 315–324. https://doi.org/10.1080/02699931.2014.999748

Carr, V. A., Viskontas, I. V., Engel, S. A., & Knowlton, B. J. (2010). Neural activity in the hippocampus and perirhinal cortex during encoding is associated with the durability of episodic memory. *Journal of Cognitive Neuroscience*, *22*(11), 2652–2662. Retrieved from http://www.mitpressjournals.org/doi/abs/10.1162/jocn.2009.21381

Carre, J. M., Fisher, P. M., Manuck, S. B., & Hariri, A. R. (2012). Interaction between trait anxiety and trait anger predict amygdala reactivity to angry facial expressions in men but not women. *Social Cognitive and Affective Neuroscience*, *7*(2), 213–221. https://doi.org/10.1093/scan/nsq101

Caspi, A. (2003). Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science*, *301*(5631), 386–389. https://doi.org/10.1126/science.1083968

Caudal, D., Godsil, B. P., Mailliet, F., Bergerot, D., & Jay, T. M. (2010). Acute Stress Induces Contrasting Changes in AMPA Receptor Subunit Phosphorylation within the Prefrontal Cortex, Amygdala and Hippocampus. *PLoS ONE*, *5*(12), e15282. https://doi.org/10.1371/journal.pone.0015282

Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Research Reviews*, *56*(1), 1–26. https://doi.org/10.1016/j.brainresrev.2007.05.002

Chan, S., & Debono, M. (2010). Review: Replication of cortisol circadian rhythm: new advances in hydrocortisone replacement therapy. *Therapeutic Advances in Endocrinology and Metabolism*, *1*(3), 129–138. Retrieved from http://tae.sagepub.com/content/1/3/129.short

Chan, S. W. Y., Goodwin, G. M., & Harmer, C. J. (2007). Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine*, *37*(9), 1281–91. https://doi.org/10.1017/S0033291707000669

Chan, S. W. Y., Norbury, R., Goodwin, G. M., & Harmer, C. J. (2009). Risk for depression and neural responses to fearful facial expressions of emotion. *The British Journal of Psychiatry*, *194*(2), 139–145. https://doi.org/10.1192/bjp.bp.107.047993

Chaouloff, F., & Groc, L. (2011). Temporal modulation of hippocampal excitatory transmission by corticosteroids and stress. *Frontiers in Neuroendocrinology*, *32*(1), 25–42. https://doi.org/10.1016/j.yfrne.2010.07.004

Charney, D. S., & Manji, H. K. (2004). Life Stress, Genes, and Depression: Multiple Pathways Lead to Increased Risk and New Opportunities for Intervention. *Science Signaling*, *2004*(225), re5-re5. https://doi.org/10.1126/stke.2252004re5

Chen, A. C., & Etkin, A. (2013). Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. *Neuropsychopharmacology*, *38*(10), 1889–1898. Retrieved from http://www.nature.com/npp/journal/v38/n10/abs/npp2013122a.html

Chen, F. S., Schmitz, J., Domes, G., Tuschen-Caffier, B., & Heinrichs, M. (2014). Effects of acute social stress on emotion processing in children. *Psychoneuroendocrinology*, *40*, 91–95. https://doi.org/10.1016/j.psyneuen.2013.11.003

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374–381. https://doi.org/10.1038/nrendo.2009.106

Ciriaco, M., Ventrice, P., Russo, G., Scicchitano, M., Mazzitello, G., Scicchitano, F., & Russo, E. (2013). Corticosteroid-related central nervous system side effects. *Journal of Pharmacology & Pharmacotherapeutics*, *4*(Supplement 1), S94–S98. https://doi.org/10.4103/0976-500X.120975

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*, *30*(2), 203–216. https://doi.org/10.1016/j.cpr.2009.11.003

Ciufolini, S., Dazzan, P., Kempton, M. J., Pariante, C. M., & Mondelli, V. (2014). HPA axis response to social stress is attenuated in schizophrenia but normal in depression: evidence from a meta-analysis of existing studies. *Neuroscience & Biobehavioral Reviews*, *47*, 359–368. Retrieved from http://www.sciencedirect.com/science/article/pii/S014976341400219X

Clark, L., Chamberlain, S. R., & Sahakian, B. J. (2009). Neurocognitive Mechanisms in Depression: Implications for Treatment. *Annual Review of Neuroscience*, *32*(1), 57–74. https://doi.org/10.1146/annurev.neuro.31.060407.125618

Clewett, D., Schoeke, A., & Mather, M. (2014). Locus coeruleus neuromodulation of memories encoded during negative or unexpected action outcomes. *Neurobiology of Learning and Memory*, *111*, 65–70. https://doi.org/10.1016/j.nlm.2014.03.006

Cohen, M. X., & Frank, M. J. (2009). Neurocomputational models of basal ganglia function in learning, memory and choice. *Behavioural Brain Research*, *199*(1), 141–156. https://doi.org/10.1016/j.bbr.2008.09.029

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*(4), 385–396.

Cole, J., Costafreda, S. G., McGuffin, P., & Fu, C. H. Y. (2011). Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders*, *134*(1–3), 483–487. https://doi.org/10.1016/j.jad.2011.05.057

Conrad, C. D. (2008). Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. *Reviews in the Neurosciences*, *19*(6), 395–412. Retrieved from http://www.degruyter.com/dg/viewarticle.fullcontentlink:pdfeventlink/$002fj$002frevneuro.2008.19.6$002frevneuro.2008.19.6.395$002frevneuro.2008.19.6.395.pdf?t:ac=j$002frevneuro.2008.19.6$002frevneuro.2008.19.6.395$002frevneuro.2008.19.6.395.xml

Conrad, C. D. (2010). A critical review of chronic stress effects on spatial learning and memory. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(5), 742–755. https://doi.org/10.1016/j.pnpbp.2009.11.003

Conway, A. R., Kane, M. J., Bunting, M. F., Hambrick, D. Z., Wilhelm, O., & Engle, R. W. (2005). Working memory span tasks: A methodological review and user's guide. *Psychonomic Bulletin & Review*, *12*(5), 769–786. Retrieved from http://link.springer.com/article/10.3758/BF03196772

Corral-Frías, N. S., Nikolova, Y. S., Michalski, L. J., Baranger, D. A. A., Hariri, A. R., & Bogdan, R. (2015). Stress-related anhedonia is associated with ventral striatum reactivity to reward and transdiagnostic psychiatric symptomatology. *Psychological Medicine*, *45*(12), 2605–2617. https://doi.org/10.1017/S0033291715000525

Correa, M. S., Balardin, J. B., Caldieraro, M. A. K., Fleck, M. P., Argimon, I., Luz, C., & Bromberg, E. (2012). Contextual recognition memory deficits in major depression are suppressed by cognitive support at encoding. *Biological Psychology*, *89*(2), 293–299. https://doi.org/10.1016/j.biopsycho.2011.11.001

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. Y. (2008). Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews*, *58*(1), 57–70. https://doi.org/10.1016/j.brainresrev.2007.10.012

Cottrell, E. C., Seckl, J., Cottrell, E. C., & Seckl, J. R. (2009). Prenatal stress, glucocorticoids and the programming of adult disease. *Frontiers in Behavioral Neuroscience*, *3*, 19. https://doi.org/10.3389/neuro.08.019.2009

Cowen, P. J. (2008). Serotonin and depression: pathophysiological mechanism or marketing myth? *Trends in Pharmacological Sciences*, *29*(9), 433–436. https://doi.org/10.1016/j.tips.2008.05.004

Cowen, P. J. (2009). Not fade away: the HPA axis and depression. *Psychological Medicine*, *40*(1), 1. https://doi.org/10.1017/S0033291709005558

Craig, A. D. (2009). How do you feel—now? the anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*(1). Retrieved from http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=1471003X&AN=35775154&h=Xhb4TcOmdjXk8ehKNBi6wqGUEl1R0mWunEr2U9Yw0G98EKEU7fMRzMJIGYf33Pk72vzMfH5WALh2HMMtzQ6prA%3D%3D&crl=c

Cranston, C. C. (2014). A Review of the Effects of Prolonged Exposure to Cortisol on the Regulation of the HPA Axis: Implications for the Development and Maintenance of Posttraumatic Stress Disorder. *The New School Psychology Bulletin*, *11*(1), 1–13. Retrieved from http://www.nspb.net/index.php/nspb/article/view/4

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., … Murphy, D. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: A functional magnetic resonance imaging study. *Human Brain Mapping*, *9*(2), 93–105. https://doi.org/10.1002/(SICI)1097-0193(200002)9:2<93::AID-HBM4>3.0.CO;2-Z

Crumeyrolle-Arias, M., Jaglin, M., Bruneau, A., Vancassel, S., Cardona, A., Daugé, V., … Rabot, S. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology*, *42*, 207–217. https://doi.org/10.1016/j.psyneuen.2014.01.014

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nature Reviews. Neuroscience*, *13*(10), 701–12. https://doi.org/10.1038/nrn3346

Cryan, J. F., & O'Mahony, S. M. (2011). The microbiome-gut-brain axis: from bowel to behavior: From bowel to behavior. *Neurogastroenterology & Motility*, *23*(3), 187–192. https://doi.org/10.1111/j.1365-2982.2010.01664.x

Cunningham-Bussel, A. C., Root, J. C., Butler, T., Tuescher, O., Pan, H., Epstein, J., … Silbersweig, D. (2009). Diurnal cortisol amplitude and fronto-limbic activity in response to stressful stimuli. *Psychoneuroendocrinology*, *34*(5), 694–704. https://doi.org/10.1016/j.psyneuen.2008.11.011

Curtis, A. L., Bello, N. T., Connolly, K. R., & Valentino, R. J. (2002). Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. *Journal of Neuroendocrinology*, *14*(8), 667–682.

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423. https://doi.org/10.1016/S1364-6613(03)00197-9

Curtis, J. R., Westfall, A. O., Allison, J., Bijlsma, J. W., Freeman, A., George, V., … Saag, K. G. (2006). Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis & Rheumatism*, *55*(3), 420–426. https://doi.org/10.1002/art.21984

Damoiseaux, J. S., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853. Retrieved from http://www.pnas.org/content/103/37/13848.short

Dayan, P., & Huys, Q. J. M. (2008). Serotonin, Inhibition, and Negative Mood. *PLoS Computational Biology*, *4*(2), e4. https://doi.org/10.1371/journal.pcbi.0040004

De Kloet, E. R., & Derijk, R. (2004). Signaling Pathways in Brain Involved in Predisposition and Pathogenesis of Stress-Related Disease: Genetic and Kinetic Factors Affecting the MR/GR Balance. *Annals of the New York Academy of Sciences*, *1032*(1), 14–34. https://doi.org/10.1196/annals.1314.003

De Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience*, *6*(6), 463–475. https://doi.org/10.1038/nrn1683

De Kloet, E. R., Karst, H., & Joëls, M. (2008). Corticosteroid hormones in the central stress response: Quick-and-slow. *Frontiers in Neuroendocrinology*, *29*(2), 268–272. https://doi.org/10.1016/j.yfrne.2007.10.002

De Kloet, E. R., Van Acker, S. A., Sibug, R. M., Oitzl, M. S., Meijer, O. C., Rahmouni, K., & De Jong, W. (2000). Brain mineralocorticoid receptors and centrally regulated functions. *Kidney International*, *57*(4), 1329–1336. Retrieved from http://www.nature.com/ki/journal/v57/n4/abs/4491468a.html

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joëls, M. (1998). Brain Corticosteroid Receptor Balance in Health and Disease 1. *Endocrine Reviews*, *19*(3), 269–301. Retrieved from http://press.endocrine.org/doi/abs/10.1210/edrv.19.3.0331

De Leon, M. J., McRae, T., Rusinek, H., Convit, A., De Santi, S., Tarshish, C., … others. (1997). Cortisol Reduces Hippocampal Glucose Metabolism in Normal Elderly, but Not in Alzheimer's Disease 1. *The Journal of Clinical Endocrinology & Metabolism*, *82*(10), 3251–3259. Retrieved from http://press.endocrine.org/doi/abs/10.1210/jcem.82.10.4305

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, *29*(4), 1359–1367. https://doi.org/10.1016/j.neuroimage.2005.08.035

de Quervain, D. J.-F., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology*, *30*(3), 358–370. https://doi.org/10.1016/j.yfrne.2009.03.002

de Quervain, D. J.-F., Henke, K., Aerni, A., Treyer, V., McGaugh, J. L., Berthold, T., … Hock, C. (2003). Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *European Journal of Neuroscience*, *17*(6), 1296–1302. https://doi.org/10.1046/j.1460-9568.2003.02542.x

de Voogd, L. D., Fernández, G., & Hermans, E. J. (2016). Disentangling the roles of arousal and amygdala activation in emotional declarative memory. *Social Cognitive and Affective Neuroscience*, *11*(9), 1471–1480. https://doi.org/10.1093/scan/nsw055

Dedovic, K., Duchesne, A., Andrews, J., Engert, V., & Pruessner, J. C. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *NeuroImage*, *47*(3), 864–871. https://doi.org/10.1016/j.neuroimage.2009.05.074

Dedovic, K., Engert, V., Duchesne, A., Lue, S. D., Andrews, J., Efanov, S. I., … Pruessner, J. C. (2010). Cortisol Awakening Response and Hippocampal Volume: Vulnerability for Major Depressive Disorder? *Biological Psychiatry*, *68*(9), 847–853. https://doi.org/10.1016/j.biopsych.2010.07.025

Delgado y Palacios, R., Verhoye, M., Henningsen, K., Wiborg, O., & Van der Linden, A. (2014). Diffusion Kurtosis Imaging and High-Resolution MRI Demonstrate Structural Aberrations of Caudate Putamen and Amygdala after Chronic Mild Stress. *PLoS ONE*, *9*(4), e95077. https://doi.org/10.1371/journal.pone.0095077

Demenescu, L. R., Kortekaas, R., Cremers, H. R., Renken, R. J., Tol, M. J. van, Wee, N. J. A. van der, … Aleman, A. (2013). Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. *Journal of Psychiatric Research*, *47*(8), 1024–1031. https://doi.org/10.1016/j.jpsychires.2013.03.020

Desmedt, A., Marighetto, A., Richter-Levin, G., & Calandreau, L. (2015). Adaptive emotional memory: the key hippocampal–amygdalar interaction. *Stress: The International Journal on the Biology of Stress*, *18*(3), 297–308.

Dias-Ferreira, E., Sousa, J. C., Melo, I., Morgado, P., Mesquita, A. R., Cerqueira, J. J., … Sousa, N. (2009). Chronic Stress Causes Frontostriatal Reorganization and Affects Decision-Making. *Science*, *325*(5940), 621–625. https://doi.org/10.1126/science.1171203

Dichter, G. S., Gibbs, D., & Smoski, M. J. (2015). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *Journal of Affective Disorders*, *172*, 8–17. https://doi.org/10.1016/j.jad.2014.09.028

Dienes, K. A., Hazel, N. A., & Hammen, C. L. (2013). Cortisol secretion in depressed, and at-risk adults. *Psychoneuroendocrinology*, *38*(6), 927–940. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453012003356

Dietrich, A., Ormel, J., Buitelaar, J. K., Verhulst, F. C., Hoekstra, P. J., & Hartman, C. A. (2013). Cortisol in the morning and dimensions of anxiety, depression, and aggression in children from a general population and clinic-referred cohort: An integrated analysis. The TRAILS study. *Psychoneuroendocrinology*, *38*(8), 1281–1298. https://doi.org/10.1016/j.psyneuen.2012.11.013

Dinan, T. G., & Cryan, J. F. (2012). Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology. *Psychoneuroendocrinology*, *37*(9), 1369–1378. https://doi.org/10.1016/j.psyneuen.2012.03.007

Dinan, T. G., Quigley, E. M. M., Ahmed, S. M. M., Scully, P., O'Brien, S., O'Mahony, L., … Keeling, P. W. N. (2006). Hypothalamic-Pituitary-Gut Axis Dysregulation in Irritable Bowel Syndrome: Plasma Cytokines as a Potential Biomarker? *Gastroenterology*, *130*(2), 304–311. https://doi.org/10.1053/j.gastro.2005.11.033

Dolcos, F. (2014). The fast and the slow sides of cortisol's effects on emotional interference and sustained attention. *Frontiers in Neuroscience*, *8*, 268. https://doi.org/10.3389/fnins.2014.00268

Dolcos, F., Diaz-Granados, P., Wang, L., & McCarthy, G. (2008). Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. *Neuropsychologia*, *46*(1), 326–335. https://doi.org/10.1016/j.neuropsychologia.2007.07.010

Dorey, R., Piérard, C., Chauveau, F., David, V., & Béracochéa, D. (2012). Stress-Induced Memory Retrieval Impairments: Different Time-Course Involvement of Corticosterone and Glucocorticoid Receptors in Dorsal and Ventral Hippocampus. *Neuropsychopharmacology*, *37*(13), 2870–2880. https://doi.org/10.1038/npp.2012.170

Douglas, J. L., & Harmer, C. J. (2011). Early morning cortisol response and emotional processing in adults exposed to postnatal depression in infancy. *European Psychiatry*, *26*(8), 479–481. https://doi.org/10.1016/j.eurpsy.2010.01.015

Dresler, M., Kluge, M., Pawlowski, M., Schüssler, P., Steiger, A., & Genzel, L. (2011). A double dissociation of memory impairments in major depression. *Journal of Psychiatric Research*, *45*(12), 1593–1599. https://doi.org/10.1016/j.jpsychires.2011.07.015

Drevets, W. C. (1999). Prefrontal Cortical-Amygdalar Metabolism in Major Depression. *Annals of the New York Academy of Sciences*, *877*(1), 614–637. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.1999.tb09292.x/full

Duman, R. S., & Monteggia, L. M. (2006). A Neurotrophic Model for Stress-Related Mood Disorders. *Biological Psychiatry*, *59*(12), 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Ekman, P., & Friesen, W. V. (1976). *Pictures offacial affect*. Palo Alto.

Eldar, E., Rutledge, R. B., Dolan, R. J., & Niv, Y. (2015). Mood as Representation of Momentum. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2015.07.010

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nature Neuroscience*, *3*(11), 1149–1152. Retrieved from http://www.nature.com/neuro/journal/v3/n11/abs/nn1100_1149.html

Ellenbogen, M. A., Schwartzman, A. E., Stewart, J., & Walker, C.-D. (2002). Stress and selective attention: The interplay of mood, cortisol levels, and emotional information processing. *Psychophysiology*, *39*(6), 723–732. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/1469-8986.3960723/abstract

Ellenbogen, M. A., Schwartzman, A., Stewart, J., & Walker, C. (2006). Automatic and effortful emotional information processing regulates different aspects of the stress response. *Psychoneuroendocrinology*, *31*(3), 373–387. https://doi.org/10.1016/j.psyneuen.2005.09.001

Elliott, R., Zahn, R., Deakin, J. F. W., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 153–82. https://doi.org/10.1038/npp.2010.77

Engel, G. L. (1979). The biopsychosocial model and the education of health professionals. *General Hospital Psychiatry*, *1*(2), 156–165. https://doi.org/10.1016/0163-8343(79)90062-8

Entis, J. J., Doerga, P., Barrett, L. F., & Dickerson, B. C. (2012). A reliable protocol for the manual segmentation of the human amygdala and its subregions using ultra-high resolution MRI. *NeuroImage*, *60*(2), 1226–1235. https://doi.org/10.1016/j.neuroimage.2011.12.073

Erickson, K., Drevets, W., & Schulkin, J. (2003). Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience & Biobehavioral Reviews*, *27*(3), 233–246. https://doi.org/10.1016/S0149-7634(03)00033-2

Eshel, N., & Roiser, J. P. (2010). Reward and Punishment Processing in Depression. *Biological Psychiatry*, *68*(2), 118–124. https://doi.org/10.1016/j.biopsych.2010.01.027

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., & Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, *44*(6), 1043–1055. Retrieved from http://www.sciencedirect.com/science/article/pii/S0896627304007913

Evans, R. M., & Arriza, J. L. (1989). A molecular framework for the actions of glucocorticoid hormones in the nervous system. *Neuron*, *2*(2), 1105–1112. https://doi.org/10.1016/0896-6273(89)90177-3

Eysenck, H., & Eysenck, S. (1975). *Manual of the Eysenck Personality Questionnaire*. London: Hodder & Stoughton.

Fairhall, S. L., Sharma, S., Magnusson, J., & Murphy, B. (2010). Memory related dysregulation of hippocampal function in major depressive disorder. *Biological Psychology*, *85*(3), 499–503. https://doi.org/10.1016/j.biopsycho.2010.09.002

Fanselow, M. S., & Dong, H.-W. (2010). Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures? *Neuron*, *65*(1), 7–19. https://doi.org/10.1016/j.neuron.2009.11.031

Faravelli, C., Lo Sauro, C., Lelli, L., Pietrini, F., Lazzeretti, L., Godini, L., … Ricca, V. (2012). The Role of Life Events and HPA Axis in Anxiety Disorders: A Review. *Current Pharmaceutical Design*, *18*(35), 5663–5674. https://doi.org/10.2174/138161212803530907

Fardet, L., Nazareth, I., Whitaker, H. J., & Petersen, I. (2013). Severe Neuropsychiatric Outcomes Following Discontinuation of Long-Term Glucocorticoid Therapy: A Cohort Study. *Journal of Clinical Psychiatry*, *74*(4), e281–e286.

Fardet, L., Petersen, I., & Nazareth, I. (2014). Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Retrieved from http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2011.11071009

Fastenrath, M., Coynel, D., Spalek, K., Milnik, A., Gschwind, L., Roozendaal, B., … de Quervain, D. J. F. (2014). Dynamic Modulation of Amygdala-Hippocampal Connectivity by Emotional Arousal. *Journal of Neuroscience*, *34*(42), 13935–13947. https://doi.org/10.1523/JNEUROSCI.0786-14.2014

Feeney, J., Gaffney, P., & O'Mara, S. M. (2012). Age and cortisol levels modulate judgment of positive and negative facial expressions. *Psychoneuroendocrinology*, *37*(6), 827–835. https://doi.org/10.1016/j.psyneuen.2011.09.015

Felmingham, K. L., Bryant, R. A., & Gordon, E. (2003). Processing angry and neutral faces in post-traumatic stress disorder: an event-related potentials study. *Neuroreport*, *14*(5), 777–780. Retrieved from http://journals.lww.com/neuroreport/Abstract/2003/04150/Processing_angry_and_neutral_faces_in.24.aspx

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., … Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proceedings of the National Academy of Sciences*, *106*(17), 7209–7214. Retrieved from http://www.pnas.org/content/106/17/7209.short

Filippini, N., Nickerson, L. D., Beckmann, C. F., Ebmeier, K. P., Frisoni, G. B., Matthews, P. M., … Mackay, C. E. (2012). Age-related adaptations of brain function during a memory task are also present at rest. *NeuroImage*, *59*(4), 3821–3828. https://doi.org/10.1016/j.neuroimage.2011.11.063

Finlay-Jones, R., & Brown, G. W. (2009). Types of stressful life event and the onset of anxiety and depressive disorders. *Psychological Medicine*, *11*(4), 803. https://doi.org/10.1017/S0033291700041301

Finsterwald, C., & Alberini, C. M. (2014). Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: From adaptive responses to psychopathologies. *Neurobiology of Learning and Memory*, *112*, 17–29. https://doi.org/10.1016/j.nlm.2013.09.017

First, M., Spitzer, R., Gibbon, M., & Williams, J. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). American Psychiatric Press.

Fischer, H. akan, Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2003). Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Research Bulletin*, *59*(5), 387–392. Retrieved from http://www.sciencedirect.com/science/article/pii/S0361923002009401

Fisher, H. L., Cohen-Woods, S., Hosang, G. M., Uher, R., Powell-Smith, G., Keers, R., … McGuffin, P. (2012). Stressful life events and the serotonin transporter gene (5-HTT) in recurrent clinical depression. *Journal of Affective Disorders*, *136*(1–2), 189–193. https://doi.org/10.1016/j.jad.2011.09.016

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., & Phan, K. L. (2006). Beyond threat: Amygdala reactivity across multiple expressions of facial affect. *NeuroImage*, *30*(4), 1441–1448. https://doi.org/10.1016/j.neuroimage.2005.11.003

Fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Simmons, A. N., Sullivan, S. G., Allard, C. B., … Stein, M. B. (2015). Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. *Psychological Medicine*, *FirstView*, 1–18. https://doi.org/10.1017/S0033291715002603

Forsythe, P., & Kunze, W. A. (2013). Voices from within: gut microbes and the CNS. *Cellular and Molecular Life Sciences*, *70*(1), 55–69. https://doi.org/10.1007/s00018-012-1028-z

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): Facts and future directions. *International Journal of Psychophysiology*, *72*(1), 67–73. https://doi.org/10.1016/j.ijpsycho.2008.03.014

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, *1*(3), 210–220. https://doi.org/10.1002/hbm.460010306

Frodl, T., Jäger, M., Smajstrlova, I., Born, I., Bottlender, R., Palladino, T., … Meisenzahl, E. M. (2008). Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *Journal of Psychiatry & Neuroscience : JPN*, *33*(5), 423–430. Retrieved from http://europepmc.org/abstract/med/18787661

Frodl, T., & O'Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of Disease*, *52*, 24–37. https://doi.org/10.1016/j.nbd.2012.03.012

Frol, A. B., Vasquez, A., Getahun, Y., Pacheco, M., Khan, D. A., & Brown, E. S. (2013). A comparison of clinician-rated neuropsychological and self-rated cognitive assessments in patients with asthma and rheumatologic disorders. In *Allergy and Asthma Proceedings* (Vol. 34, p. 170). OceanSide Publications. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3587715/

Fu, C. H. Y., Williams, S. C. ., Cleare, A. J., Brammer, M. J., Walsh, N. D., Kim, J. K., … Bullmore, E. T. (2004). Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment: A Prospective, Event-Related Functional Magnetic Resonance Imaging Study. *Archives of General Psychiatry*, *61*(9), 877–889.

Fuchs, E., & Flügge, G. (1998). Stress, glucocorticoids and structural plasticity of the hippocampus. *Neuroscience & Biobehavioral Reviews*, *23*(2), 295–300. Retrieved from http://www.sciencedirect.com/science/article/pii/S0149763498000311

Gądek-Michalska, A., Spyrka, J., Rachwalska, P., Tadeusz, J., & Bugajski, J. (2013). Influence of chronic stress on brain corticosteroid receptors and HPA axis activity. *Pharmacological Reports*, *65*(5), 1163–1175. Retrieved from http://www.sciencedirect.com/science/article/pii/S1734114013714749

Gagnon, S. A., & Wagner, A. D. (2016). Acute stress and episodic memory retrieval: Neurobiological mechanisms and behavioral consequences. *Annals of the New York Academy of Sciences*, *1369*(1), 55–75. https://doi.org/10.1111/nyas.12996

Gareau, M. G., Jury, J., MacQueen, G., Sherman, P. M., & Perdue, M. H. (2007). Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut*, *56*(11), 1522–1528. https://doi.org/10.1136/gut.2006.117176

Gareau, M. G., Sherman, P. M., & Walker, W. A. (2010). Probiotics and the gut microbiota in intestinal health and disease. *Nature Reviews Gastroenterology & Hepatology*, *7*(9), 503–514. https://doi.org/10.1038/nrgastro.2010.117

Garrett, A., Kelly, R., Gomez, R., Keller, J., Schatzberg, A. F., & Reiss, A. L. (2014). Aberrant brain activation during a working memory task in psychotic major depression. *American Journal of Psychiatry*. Retrieved from http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2010.09121718

Garrett, N., Sharot, T., Faulkner, P., Korn, C. W., Roiser, J. P., & Dolan, R. J. (2014). Losing the rose tinted glasses: neural substrates of unbiased belief updating in depression. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00639

Garvert, M. M., Friston, K. J., Dolan, R. J., & Garrido, M. I. (2014). Subcortical amygdala pathways enable rapid face processing. *NeuroImage*, *102*, *Part 2*, 309–316. https://doi.org/10.1016/j.neuroimage.2014.07.047

Gentili, C., Cristea, I. A., Angstadt, M., Klumpp, H., Tozzi, L., Phan, K. L., & Pietrini, P. (2016). Beyond emotions: A meta-analysis of neural response within face processing system in social anxiety. *Experimental Biology and Medicine*, *241*(3), 225–237. https://doi.org/10.1177/1535370215603514

Gift, A. G., Wood, R. M., & Cahill, C. A. (1989). Depression, somatization and steroid use in chronic obstructive pulmonary disease. *International Journal of Nursing Studies*, *26*(2), 281–286.

Godlewska, B. R., Norbury, R., Selvaraj, S., Cowen, P. J., & Harmer, C. J. (2012). Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychological Medicine*, *42*(12), 2609–2617. https://doi.org/10.1017/S0033291712000591

Gohier, B., Ferracci, L., Surguladze, S. A., Lawrence, E., El Hage, W., Kefi, M. Z., … Le Gall, D. (2009). Cognitive inhibition and working memory in unipolar depression. *Journal of Affective Disorders*, *116*(1–2), 100–105. https://doi.org/10.1016/j.jad.2008.10.028

Goode, T. D., Leong, K.-C., Goodman, J., Maren, S., & Packard, M. G. (2016). Enhancement of striatum-dependent memory by conditioned fear is mediated by beta-adrenergic receptors in the basolateral amygdala. *Neurobiology of Stress*, *3*, 74–82. https://doi.org/10.1016/j.ynstr.2016.02.004

Goodyer, I. M. (2015). Genes, environments and depressions in young people. *Archives of Disease in Childhood*, *100*(11), 1064–1069. https://doi.org/10.1136/archdischild-2014-306936

Goodyer, I. M., Bacon, A., Ban, M., Croudace, T., & Herbert, J. (2009). Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. *The British Journal of Psychiatry*, *195*(1), 39–45. https://doi.org/10.1192/bjp.bp.108.054775

Goodyer, I. M., Herbert, J., Tamplin, A., Secher, S. M., & Pearson, J. (1997). Short-Term Outcome of Major Depression: II. Life Events, Family Dysfunction, and Friendship Difficulties as Predictors of Persistent Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(4), 474–480.

Goodyer, I. M., Tamplin, A., Herbert, J., & Altham, P. M. E. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *The British Journal of Psychiatry*, *177*(6), 499–504. Retrieved from http://bjp.rcpsych.org/content/177/6/499.short

Gotlib, I. H., Joormann, J., Minor, K. L., & Hallmayer, J. (2008). HPA Axis Reactivity: A Mechanism Underlying the Associations Among 5-HTTLPR, Stress, and Depression. *Biological Psychiatry*, *63*(9), 847–851. https://doi.org/10.1016/j.biopsych.2007.10.008

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology*, *113*(1), 127. Retrieved from http://psycnet.apa.org/journals/abn/113/1/127/

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010a). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*(4), 831–853. https://doi.org/10.1016/j.neuropsychologia.2010.01.001

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010b). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*(4), 831–853. https://doi.org/10.1016/j.neuropsychologia.2010.01.001

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2009). The role of the basal ganglia in learning and memory: Neuropsychological studies. *Behavioural Brain Research*, *199*(1), 53–60. https://doi.org/10.1016/j.bbr.2008.11.020

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, *62*(5), 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253–258. Retrieved from http://www.pnas.org/content/100/1/253.short

Grimm, S., Weigand, A., Kazzer, P., Jacobs, A. M., & Bajbouj, M. (2012). Neural mechanisms underlying the integration of emotion and working memory. *NeuroImage*, *61*(4), 1188–1194. https://doi.org/10.1016/j.neuroimage.2012.04.004

Groeneweg, F. L., Karst, H., De Kloet, E. R., & Joëls, M. (2012). Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. *Molecular and Cellular Endocrinology*, *350*(2), 299–309. https://doi.org/10.1016/j.mce.2011.06.020

Grynderup, M. B., Kolstad, H. A., Mikkelsen, S., Andersen, J. H., Bonde, J. P., Buttenschøn, H. N., … Hansen, Å. M. (2013). A two-year follow-up study of salivary cortisol concentration and the risk of depression. *Psychoneuroendocrinology*, *38*(10), 2042–2050. https://doi.org/10.1016/j.psyneuen.2013.03.013

Guidotti, G., Calabrese, F., Anacker, C., Racagni, G., Pariante, C. M., & Riva, M. A. (2013). Glucocorticoid receptor and FKBP5 expression is altered following exposure to chronic stress: modulation by antidepressant treatment. *Neuropsychopharmacology*, *38*(4), 616–627. Retrieved from http://www.nature.com/articles/doi:10.1038%2Fnpp.2012.225

Gunduz-Bruce, H., Szeszko, P. R., Gueorguieva, R., Ashtari, M., Robinson, D. G., Kane, J. M., & Bilder, R. M. (2007). Cortisol levels in relation to hippocampal sub-regions in subjects with first episode schizophrenia. *Schizophrenia Research*, *94*(1–3), 281–287. https://doi.org/10.1016/j.schres.2007.03.025

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., … Gur, R. C. (2002). An fMRI Study of Facial Emotion Processing in Patients With Schizophrenia. *American Journal of Psychiatry*, *159*(12), 1992–1999. https://doi.org/10.1176/appi.ajp.159.12.1992

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., … Lanzenberger, R. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *NeuroImage*, *56*(3), 881–889. https://doi.org/10.1016/j.neuroimage.2011.02.064

Hall, B. S., Moda, R. N., & Liston, C. (2015). Glucocorticoid mechanisms of functional connectivity changes in stress-related neuropsychiatric disorders. *Neurobiology of Stress*, *1*, 174–183. https://doi.org/10.1016/j.ynstr.2014.10.008

Hamilton, J. P., & Gotlib, I. H. (2008). Neural Substrates of Increased Memory Sensitivity for Negative Stimuli in Major Depression. *Biological Psychiatry*, *63*(12), 1155–1162. https://doi.org/10.1016/j.biopsych.2007.12.015

Hardeveld, F., Spijker, J., Vreeburg, S. A., Graaf, R. D., Hendriks, S. M., Licht, C. M. M., … Beekman, A. T. F. (2014). Increased cortisol awakening response was associated with time to recurrence of major depressive disorder. *Psychoneuroendocrinology*, *50*, 62–71. https://doi.org/10.1016/j.psyneuen.2014.07.027

Harmer, C. J. (2008). Serotonin and emotional processing: Does it help explain antidepressant drug action? *Neuropharmacology*, *55*(6), 1023–1028. https://doi.org/10.1016/j.neuropharm.2008.06.036

Harmer, C. J. (2010). Antidepressant drug action: a neuropsychological perspective. *Depression and Anxiety*, *27*(3), 231–233. https://doi.org/10.1002/da.20680

Harmer, C. J., Bhagwagar, Z., Perrett, D. I., Völlm, B. A., Cowen, P. J., & Goodwin, G. M. (2003). Acute SSRI Administration Affects the Processing of Social Cues in Healthy Volunteers. *Neuropsychopharmacology*, *28*(1), 148–152. https://doi.org/10.1038/sj.npp.1300004

Harmer, C. J., Cowen, P. J., & Goodwin, G. M. (2011). Efficacy markers in depression. *Journal of Psychopharmacology (Oxford, England)*, *25*(9), 1148–58. https://doi.org/10.1177/0269881110367722

Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *The British Journal of Psychiatry : The Journal of Mental Science*, *195*(2), 102–8. https://doi.org/10.1192/bjp.bp.108.051193

Harmer, C. J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., … Cowen, P. (2009). Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry*, *166*(10), 1178–1184. Retrieved from http://ps.psychiatryonline.org/article.aspx?articleid=101229&RelatedWidgetArticles=true

Harmer, C. J., Shelley, N. C., Cowen, P. J., & Goodwin, G. M. (2004). Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry*, *161*(7), 1256–1263. Retrieved from http://journals.psychiatryonline.org/article.aspx?articleid=176920

Heim, C., Bradley, B., Mletzko, T., Deveau, T. C., Musselmann, D. L., Nemeroff, C. B., … Binder, E. B. (2009). Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by CRH receptor 1 gene. *Frontiers in Behavioral Neuroscience*, *3*, 41. https://doi.org/10.3389/neuro.08.041.2009

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry*, *49*(12), 1023–1039. Retrieved from http://www.sciencedirect.com/science/article/pii/S000632230101157X

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology*, *33*(6), 693–710. https://doi.org/10.1016/j.psyneuen.2008.03.008

Heinzel, A., Northoff, G., Boeker, H., Boesiger, P., & Grimm, S. (2010). Emotional processing and executive functions in major depressive disorder: dorsal prefrontal activity correlates with performance in the intra–extra dimensional set shift. *Acta Neuropsychiatrica*, *22*(6), 269–279. https://doi.org/10.1111/j.1601-5215.2010.00494.x

Henckens, M. J., Klumpers, F., Everaerd, D., Kooijman, S. C., van Wingen, G. A., & Fernández, G. (2015). Inter-individual differences in stress sensitivity: Basal and stress-induced cortisol levels differentially predict neural vigilance processing under stress. *Social Cognitive and Affective Neuroscience*, nsv149. Retrieved from http://scan.oxfordjournals.org/content/early/2015/12/13/scan.nsv149.abstract

Henckens, M. J., van der Marel, K., van der Toorn, A., Pillai, A. G., Fernández, G., Dijkhuizen, R. M., & Joëls, M. (2015). Stress-induced alterations in large-scale functional networks of the rodent brain. *NeuroImage*, *105*, 312–322. https://doi.org/10.1016/j.neuroimage.2014.10.037

Henckens, M. J., van Wingen, G. A., Joels, M., & Fernandez, G. (2010). Time-Dependent Effects of Corticosteroids on Human Amygdala Processing. *Journal of Neuroscience*, *30*(38), 12725–12732. https://doi.org/10.1523/JNEUROSCI.3112-10.2010

Henckens, M. J., van Wingen, G. A., Joëls, M., & Fernández, G. (2012). Time-dependent effects of cortisol on selective attention and emotional interference: a functional MRI study. *Frontiers in Integrative Neuroscience*, *6*. https://doi.org/10.3389/fnint.2012.00066

Herbert, J. (2012). Cortisol and depression: three questions for psychiatry. *Psychological Medicine*, *43*(3), 449–469. https://doi.org/10.1017/S0033291712000955

Herman, J. P. (2013). Neural control of chronic stress adaptation. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00061

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, *24*(3), 151–180. https://doi.org/10.1016/j.yfrne.2003.07.001

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(8), 1201–1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Hermans, E. J., Battaglia, F. P., Atsak, P., de Voogd, L. D., Fernández, G., & Roozendaal, B. (2014). How the amygdala affects emotional memory by altering brain network properties. *Neurobiology of Learning and Memory*, *112*, 2–16. https://doi.org/10.1016/j.nlm.2014.02.005

Hermans, E. J., van Marle, H. J. F., Ossewaarde, L., Henckens, M. J., Qin, S., van Kesteren, M. T. R., … Fernandez, G. (2011). Stress-Related Noradrenergic Activity Prompts Large-Scale Neural Network Reconfiguration. *Science*, *334*(6059), 1151–1153. https://doi.org/10.1126/science.1209603

Herringa, R., Phillips, M., Almeida, J., Insana, S., & Germain, A. (2012). Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans. *Psychiatry Research: Neuroimaging*, *203*(2–3), 139–145. https://doi.org/10.1016/j.pscychresns.2012.02.005

Hesse, E., Mikulan, E., Decety, J., Sigman, M., Garcia, M. del C., Silva, W., … Ibanez, A. (2016). Early detection of intentional harm in the human amygdala. *Brain*, *139*(1), 54–61. https://doi.org/10.1093/brain/awv336

Heuser, I., Bissette, G., Dettling, M., Schweiger, U., Gotthardt, U., Schmider, J., … Holsboer, F. (1998). Cerebrospinal fluid concentrations of corticotropin-releasing hormone, vasopressin, and somatostatin in depressed patients and healthy controls: Response to amitriptyline treatment. *Depression and Anxiety*, *8*(2), 71–79. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1520-6394(1998)8:2%3C71::AID-DA5%3E3.0.CO;2-N/full

Holmes, A., & Wellman, C. L. (2009). Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience & Biobehavioral Reviews*, *33*(6), 773–783. https://doi.org/10.1016/j.neubiorev.2008.11.005

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, *23*(5), 477–501. Retrieved from http://www.nature.com/npp/journal/v23/n5/abs/1395567a.html

Holsboer, F. (2001). Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy. *Journal of Affective Disorders*, *62*(1), 77–91. Retrieved from http://www.sciencedirect.com/science/article/pii/S0165032700003529

Holsboer, F., & Ising, M. (2008). Central CRH system in depression and anxiety — Evidence from clinical studies with CRH1 receptor antagonists. *European Journal of Pharmacology*, *583*(2–3), 350–357. https://doi.org/10.1016/j.ejphar.2007.12.032

Holt, D. J., Kunkel, L., Weiss, A. P., Goff, D. C., Wright, C. I., Shin, L. M., … Heckers, S. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia Research*, *82*(2–3), 153–162. https://doi.org/10.1016/j.schres.2005.09.021

Holt, R. J., Graham, J. M., Whitaker, K. J., Hagan, C. C., Ooi, C., Wilkinson, P. O., … Suckling, J. (2016). Functional MRI of emotional memory in adolescent depression. *Developmental Cognitive Neuroscience*, *19*, 31–41. https://doi.org/10.1016/j.dcn.2015.12.013

Hori, H., Teraishi, T., Ota, M., Hattori, K., Matsuo, J., Kinoshita, Y., … Kunugi, H. (2014). Psychological coping in depressed outpatients: Association with cortisol response to the

combined dexamethasone/CRH test. *Journal of Affective Disorders*, *152*, 441–447. https://doi.org/10.1016/j.jad.2013.10.013

Hruschka, D. J., Kohrt, B. A., & Worthman, C. M. (2005). Estimating between- and within-individual variation in cortisol levels using multilevel models. *Psychoneuroendocrinology*, *30*(7), 698–714. https://doi.org/10.1016/j.psyneuen.2005.03.002

Hsu, D. T., Langenecker, S. A., Kennedy, S. E., Zubieta, J.-K., & Heitzeg, M. M. (2010). fMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder. *Psychiatry Research: Neuroimaging*, *183*(3), 202–208. https://doi.org/10.1016/j.pscychresns.2009.12.002

Huang, X., Huang, P., Li, D., Zhang, Y., Wang, T., Mu, J., … Xie, P. (2014). Early brain changes associated with psychotherapy in major depressive disorder revealed by resting-state fMRI: Evidence for the top-down regulation theory. *International Journal of Psychophysiology*, *94*(3), 437–444. https://doi.org/10.1016/j.ijpsycho.2014.10.011

Jackson, M. E., & Moghaddam, B. (2006). Distinct patterns of plasticity in prefrontal cortex neurons that encode slow and fast responses to stress. *European Journal of Neuroscience*, *24*(6), 1702–1710. https://doi.org/10.1111/j.1460-9568.2006.05054.x

Jackson, O., & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *NeuroImage*, *21*(1), 456–462. https://doi.org/10.1016/j.neuroimage.2003.09.050

Jagannath, A., Peirson, S. N., & Foster, R. G. (2013). Sleep and circadian rhythm disruption in neuropsychiatric illness. *Current Opinion in Neurobiology*, *23*(5), 888–894. https://doi.org/10.1016/j.conb.2013.03.008

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*(7534), 284–292. https://doi.org/10.1038/nature14188

Jankord, R., & Herman, J. P. (2008). Limbic Regulation of Hypothalamo-Pituitary-Adrenocortical Function during Acute and Chronic Stress. *Annals of the New York Academy of Sciences*, *1148*(1), 64–73. https://doi.org/10.1196/annals.1410.012

Jedema, H. P. (2004). Corticotropin-Releasing Hormone Directly Activates Noradrenergic Neurons of the Locus Ceruleus Recorded In Vitro. *Journal of Neuroscience*, *24*(43), 9703–9713. https://doi.org/10.1523/JNEUROSCI.2830-04.2004

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Joëls, M. (2011). Impact of glucocorticoids on brain function: Relevance for mood disorders. *Psychoneuroendocrinology*, *36*(3), 406–414. https://doi.org/10.1016/j.psyneuen.2010.03.004

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience*, *10*(6), 459–466. Retrieved from http://www.nature.com/nrn/journal/v10/n6/abs/nrn2632.html

Joëls, M., Fernandez, G., & Roozendaal, B. (2011). Stress and emotional memory: a matter of timing. *Trends in Cognitive Sciences*, *15*(6), 280–288. https://doi.org/10.1016/j.tics.2011.04.004

Joëls, M., Karst, H., Derijk, R., & De Kloet, E. R. (2008). The coming out of the brain mineralocorticoid receptor. *Trends in Neurosciences*, *31*(1), 1–7. https://doi.org/10.1016/j.tins.2007.10.005

Joëls, M., Karst, H., Krugers, H. J., & Lucassen, P. J. (2007). Chronic stress: Implications for neuronal morphology, function and neurogenesis. *Frontiers in Neuroendocrinology*, *28*(2–3), 72–96. https://doi.org/10.1016/j.yfrne.2007.04.001

Joëls, M., Pasricha, N., & Karst, H. (2013). The interplay between rapid and slow corticosteroid actions in brain. *European Journal of Pharmacology*, *719*(1–3), 44–52. https://doi.org/10.1016/j.ejphar.2013.07.015

Joëls, M., Sarabdjitsingh, R. A., & Karst, H. (2012). Unraveling the Time Domains of Corticosteroid Hormone Influences on Brain Activity: Rapid, Slow, and Chronic Modes. *Pharmacological Reviews*, *64*(4), 901–938. https://doi.org/10.1124/pr.112.005892

Johar, H., Emeny, R. T., Bidlingmaier, M., Lacruz, M. E., Reincke, M., Peters, A., … Ladwig, K.-H. (2015). Lower morning to evening cortisol ratio is associated with cognitive impairment in men but not women: An analysis of 733 older subjects of the cross-sectional KORA-Age study. *Psychoneuroendocrinology*, *51*, 296–306. https://doi.org/10.1016/j.psyneuen.2014.10.011

Johnson, D. A., Grant, E. J., Ingram, C. D., & Gartside, S. E. (2007). Glucocorticoid Receptor Antagonists Hasten and Augment Neurochemical Responses to a Selective Serotonin Reuptake Inhibitor Antidepressant. *Biological Psychiatry*, *62*(11), 1228–1235. https://doi.org/10.1016/j.biopsych.2007.05.003

Johnson, L. R., Farb, C., Morrison, J. H., McEwen, B. S., & Ledoux, J. E. (2005). Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience*, *136*(1), 289–299. https://doi.org/10.1016/j.neuroscience.2005.06.050

Judd, L. L., Schettler, P. J., Brown, E. S., Wolkowitz, O. M., Sternberg, E. M., Bender, B. G., … others. (2014). Adverse Consequences of Glucocorticoid Medication: Psychological, Cognitive, and Behavioral Effects. *American Journal of Psychiatry*, *171*(10), 1045–1051. Retrieved from http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2014.13091264

Jung, C., Greco, S., Nguyen, H. H., Ho, J. T., Lewis, J. G., Torpy, D. J., & Inder, W. J. (2014). Plasma, salivary and urinary cortisol levels following physiological and stress doses of hydrocortisone in normal volunteers. *BMC Endocrine Disorders*, *14*(1), 91. Retrieved from http://www.biomedcentral.com/1472-6823/14/91/

Kalafatakis, K., Russell, G. M., Harmer, C. J., Munafo, M. R., Marchant, N., Wilson, A., … Lightman, S. L. (2016). Effects of the pattern of glucocorticoid replacement on neural processing, emotional reactivity and well-being in healthy male individuals: study protocol for a randomised controlled trial. *Trials*, *17*(1). https://doi.org/10.1186/s13063-016-1159-x

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *361*(1476), 2109–2128. https://doi.org/10.1098/rstb.2006.1934

Karst, H., Berger, S., Erdmann, G., Schutz, G., & Joels, M. (2010). Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proceedings of the National Academy of Sciences*, *107*(32), 14449–14454. https://doi.org/10.1073/pnas.0914381107

Karst, H., Berger, S., Turiault, M., Tronche, F., Schütz, G., & Joëls, M. (2005). Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(52), 19204–19207. Retrieved from http://www.pnas.org/content/102/52/19204.short

Karst, H., Nair, S., Velzing, E., Rumpff-van Essen, L., Slagter, E., Shinnick-Gallagher, P., & Joëls, M. (2002). Glucocorticoids alter calcium conductances and calcium channel subunit expression in basolateral amygdala neurons. *European Journal of Neuroscience*, *16*(6), 1083–1089. https://doi.org/10.1046/j.1460-9568.2002.02172.x

Keedwell, P. A., Drapier, D., Surguladze, S. A., Giampietro, V., Brammer, M., & Phillips, M. (2010). Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression☆. *Journal of Affective Disorders*, *120*(1–3), 120–125. https://doi.org/10.1016/j.jad.2009.04.031

Keller, J., Flores, B., Gomez, R. G., Solvason, H. B., Kenna, H., Williams, G. H., & Schatzberg, A. F. (2006). Cortisol Circadian Rhythm Alterations in Psychotic Major Depression. *Biological Psychiatry*, *60*(3), 275–281. https://doi.org/10.1016/j.biopsych.2005.10.014

Kemp, A. H., & Felmingham, K. L. (2008). The psychology and neuroscience of depression and anxiety: towards an integrative model of emotion disorders. *Psychology and Neuroscience*, *1*(2), 177–181. https://doi.org/10.3922/j.psns.2008.2.010

Kendler, K. S., & Gardner, C. O. (2011). A longitudinal etiologic model for symptoms of anxiety and depression in women. *Psychological Medicine*, *41*(10), 2035–2045. https://doi.org/10.1017/S0033291711000225

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry*, *52*(5), 374–383.

Kennedy, P. J., Clarke, G., Quigley, E. M. M., Groeger, J. A., Dinan, T. G., & Cryan, J. F. (2012). Gut memories: Towards a cognitive neurobiology of irritable bowel syndrome. *Neuroscience & Biobehavioral Reviews*, *36*(1), 310–340. https://doi.org/10.1016/j.neubiorev.2011.07.001

Kerestes, R., Ladouceur, C. D., Meda, S., Nathan, P. J., Blumberg, H. P., Maloney, K., … Phillips, M. L. (2012). Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. *Psychological Medicine*, *42*(1), 29–40. https://doi.org/10.1017/S0033291711001097

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders*, *74*(1), 5–13. https://doi.org/10.1016/S0165-0327(02)00426-3

Kiem, S. A., Andrade, K. C., Spoormaker, V. I., Holsboer, F., Czisch, M., & Sämann, P. G. (2013). Resting state functional MRI connectivity predicts hypothalamus-pituitary-axis status in healthy males. *Psychoneuroendocrinology*, *38*(8), 1338–1348. https://doi.org/10.1016/j.psyneuen.2012.11.021

Kilpatrick, L. A., Zald, D. H., Pardo, J. V., & Cahill, L. F. (2006). Sex-related differences in amygdala functional connectivity during resting conditions. *NeuroImage*, *30*(2), 452–461. https://doi.org/10.1016/j.neuroimage.2005.09.065

Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *NeuroImage*, *20*(4), 2091–2099. https://doi.org/10.1016/j.neuroimage.2003.08.006

Kim, J. J., Lee, H. J., Han, J.-S., & Packard, M. G. (2001). Amygdala Is Critical for Stress-Induced Modulation of Hippocampal Long-Term Potentiation and Learning. *The Journal of Neuroscience*, *21*(14), 5222–5228. Retrieved from http://www.jneurosci.org/content/21/14/5222

Kircanski, K., & Gotlib, I. H. (2015). Processing of Emotional Information in Major Depressive Disorder: Toward a Dimensional Understanding. *Emotion Review*, 1754073915575402. https://doi.org/10.1177/1754073915575402

Kishi, T., Tsumori, T., Yokota, S., & Yasui, Y. (2006). Topographical projection from the hippocampal formation to the amygdala: A combined anterograde and retrograde tracing study in the rat. *The Journal of Comparative Neurology*, *496*(3), 349–368. https://doi.org/10.1002/cne.20919

Kitayama, N., Vaccarino, V., Kutner, M., Weiss, P., & Bremner, J. D. (2005). Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: A meta-analysis. *Journal of Affective Disorders*, *88*(1), 79–86. https://doi.org/10.1016/j.jad.2005.05.014

Kjelstrup, K. G., Tuvnes, F. A., Steffenach, H.-A., Murison, R., Moser, E. I., & Moser, M.-B. (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences*, *99*(16), 10825–10830. https://doi.org/10.1073/pnas.152112399

Knorr, U., Vinberg, M., Kessing, L. V., & Wetterslev, J. (2010). Salivary cortisol in depressed patients versus control persons: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *35*(9), 1275–1286. https://doi.org/10.1016/j.psyneuen.2010.04.001

Kober, H., Barrett, L. F., Joseph, J., Bliss-Moreau, E., Lindquist, K., & Wager, T. D. (2008). Functional grouping and cortical–subcortical interactions in emotion: A meta-analysis of neuroimaging studies. *NeuroImage*, *42*(2), 998–1031. https://doi.org/10.1016/j.neuroimage.2008.03.059

Koster, E. H. W., Crombez, G., Verschuere, B., & De Houwer, J. (2004). Selective attention to threat in the dot probe paradigm: differentiating vigilance and difficulty to disengage. *Behaviour Research and Therapy*, *42*(10), 1183–1192. https://doi.org/10.1016/j.brat.2003.08.001

Koster, E. H. W., Verschuere, B., Crombez, G., & Van Damme, S. (2005). Time-course of attention for threatening pictures in high and low trait anxiety. *Behaviour Research and Therapy*, *43*(8), 1087–1098. https://doi.org/10.1016/j.brat.2004.08.004

Kozlovskiy, S. A., Pyasik, M. M., Korotkova, A. V., Vartanov, A. V., Glozman, J. M., & Kiselnikov, A. A. (2014). Activation of left lingual gyrus related to working memory for schematic faces. *International Journal of Psychophysiology*, *94*(2), 241. https://doi.org/10.1016/j.ijpsycho.2014.08.928

Kret, M. E., & Ploeger, A. (2015). Emotion processing deficits: A liability spectrum providing insight into comorbidity of mental disorders. *Neuroscience & Biobehavioral Reviews*, *52*, 153–171. https://doi.org/10.1016/j.neubiorev.2015.02.011

Krieglmeyer, R., & Deutsch, R. (2013). Approach Does Not Equal Approach Angry Facial Expressions Evoke Approach Only When It Serves Aggression. *Social Psychological and Personality Science*, *4*(5), 607–614. https://doi.org/10.1177/1948550612471060

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894–902. https://doi.org/10.1038/nature07455

Kühn, S., & Gallinat, J. (2013). Resting-State Brain Activity in Schizophrenia and Major Depression: A Quantitative Meta-Analysis. *Schizophrenia Bulletin*, *39*(2), 358–365. https://doi.org/10.1093/schbul/sbr151

Kukolja, J., Klingmüller, D., Maier, W., Fink, G. R., & Hurlemann, R. (2011). Noradrenergic-glucocorticoid modulation of emotional memory encoding in the human hippocampus. *Psychological Medicine*, *41*(10), 2167–2176. https://doi.org/10.1017/S0033291711000183

Kunz-Ebrecht, S. R., Kirschbaum, C., Marmot, M., & Steptoe, A. (2004). Differences in cortisol awakening response on work days and weekends in women and men from the Whitehall II cohort. *Psychoneuroendocrinology*, *29*(4), 516–528. https://doi.org/10.1016/S0306-4530(03)00072-6

Lai, C.-H., & Hsu, Y.-Y. (2011). A subtle grey-matter increase in first-episode, drug-naive major depressive disorder with panic disorder after 6 weeks' duloxetine therapy. *International Journal of Neuropsychopharmacology*, *14*(2), 225–235. https://doi.org/10.1017/S1461145710000829

Lamers, F., Vogelzangs, N., Merikangas, K. R., de Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2013). Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular Psychiatry*, *18*(6), 692–699. https://doi.org/10.1038/mp.2012.144

Langenecker, S. A., Weisenbach, S. L., Giordani, B., Briceño, E. M., Guidotti Breting, L. M., Schallmo, M.-P., … Starkman, M. N. (2012). Impact of chronic hypercortisolemia on affective processing. *Neuropharmacology*, *62*(1), 217–225. https://doi.org/10.1016/j.neuropharm.2011.07.006

Larson, C. L., Nitschke, J. B., & Davidson, R. J. (2007). Common and distinct patterns of affective response in dimensions of anxiety and depression. *Emotion*, *7*(1), 182–191. https://doi.org/10.1037/1528-3542.7.1.182

Lee, B.-T., Seok, J.-H., Lee, B.-C., Cho, S. W., Yoon, B.-J., Lee, K.-U., … Ham, B.-J. (2008). Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(3), 778–785. https://doi.org/10.1016/j.pnpbp.2007.12.009

Lee, B.-T., Seong Whi Cho, Hyung Soo Khang, Lee, B.-C., Choi, I.-G., In Kyoon Lyoo, & Ham, B.-J. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(7), 1487–1492. https://doi.org/10.1016/j.pnpbp.2007.06.030

Leonard, B. E. (2005). The HPA and immune axes in stress: the involvement of the serotonergic system. *European Psychiatry*, *20*, 302–306.

Leppänen, J. M. (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*(1), 34–39. Retrieved from http://journals.lww.com/co-psychiatry/Abstract/2006/01000/Emotional_information_processing_in_mood.7.aspx

Leshikar, E. D., Duarte, A., & Hertzog, C. (2012). Task-Selective Memory Effects for Successfully Implemented Encoding Strategies. *PLOS ONE*, *7*(5), e38160. https://doi.org/10.1371/journal.pone.0038160

Lethbridge, R., & Allen, N. B. (2008). Mood induced cognitive and emotional reactivity, life stress, and the prediction of depressive relapse. *Behaviour Research and Therapy*, *46*(10), 1142–1150. https://doi.org/10.1016/j.brat.2008.06.011

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*, *30*(10), 939–946. https://doi.org/10.1016/j.psyneuen.2005.03.013

Lewis, G., Jones, P. B., & Goodyer, I. M. (2016). The ROOTS study: a 10-year review of findings on adolescent depression, and recommendations for future longitudinal research. *Social Psychiatry and Psychiatric Epidemiology*, *51*(2), 161–170. https://doi.org/10.1007/s00127-015-1150-y

Li, M., Huang, C., Deng, W., Ma, X., Han, Y., Wang, Q., … Li, T. (2015). Contrasting and convergent patterns of amygdala connectivity in mania and depression: A resting-state study. *Journal of Affective Disorders*, *173*, 53–58. https://doi.org/10.1016/j.jad.2014.10.044

Li, S., Weerda, R., Milde, C., Wolf, O. T., & Thiel, C. M. (2014). Effects of acute psychosocial stress on neural activity to emotional and neutral faces in a face recognition memory paradigm. *Brain Imaging and Behavior*, *8*(4), 598–610. https://doi.org/10.1007/s11682-013-9287-3

Li, S.-X., Liu, L.-J., Xu, L.-Z., Gao, L., Wang, X.-F., Zhang, J.-T., & Lu, L. (2013). Diurnal alterations in circadian genes and peptides in major depressive disorder before and after escitalopram treatment. *Psychoneuroendocrinology*, *38*(11), 2789–2799. https://doi.org/10.1016/j.psyneuen.2013.07.009

Lightman, S. L. (2008). The Neuroendocrinology of Stress: A Never Ending Story. *Journal of Neuroendocrinology*, *20*(6), 880–884. https://doi.org/10.1111/j.1365-2826.2008.01711.x

Lindquist, K. A., & Barrett, L. F. (2012). A functional architecture of the human brain: emerging insights from the science of emotion. *Trends in Cognitive Sciences*, *16*(11), 533–540. https://doi.org/10.1016/j.tics.2012.09.005

Lingawi, N. W., & Balleine, B. W. (2012). Amygdala Central Nucleus Interacts with Dorsolateral Striatum to Regulate the Acquisition of Habits. *Journal of Neuroscience*, *32*(3), 1073–1081. https://doi.org/10.1523/JNEUROSCI.4806-11.2012

Lisman, J. E., & Grace, A. A. (2005). The Hippocampal-VTA Loop: Controlling the Entry of Information into Long-Term Memory. *Neuron*, *46*(5), 703–713. https://doi.org/10.1016/j.neuron.2005.05.002

Liston, C., McEwen, B. S., & Casey, B. J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(3), 912–7. https://doi.org/10.1073/pnas.0807041106

Liu, N., Hadj-Bouziane, F., Jones, K. B., Turchi, J. N., Averbeck, B. B., & Ungerleider, L. G. (2015). Oxytocin modulates fMRI responses to facial expression in macaques. *Proceedings*

of the National Academy of Sciences, *112*(24), E3123–E3130. https://doi.org/10.1073/pnas.1508097112

Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, M. (2009). Structural brain abnormalities in major depressive disorder: A selective review of recent MRI studies. *Journal of Affective Disorders*, *117*(1–2), 1–17. https://doi.org/10.1016/j.jad.2008.11.021

Lovallo, W. R., Robinson, J. L., Glahn, D. C., & Fox, P. T. (2010). Acute effects of hydrocortisone on the human brain: An fMRI study. *Psychoneuroendocrinology*, *35*(1), 15–20. https://doi.org/10.1016/j.psyneuen.2009.09.010

Luethi, M. (2008). Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. *Frontiers in Behavioral Neuroscience*, *2*. https://doi.org/10.3389/neuro.08.005.2008

Lui, S., Wu, Q., Qiu, L., Yang, X., Kuang, W., Chan, R. C., … Gong, Q. (2014). Resting-state functional connectivity in treatment-resistant depression. *American Journal of Psychiatry*. Retrieved from http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2010.10101419

Lupien, S. J. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, *1*(1).

Lupien, S. J., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose–response study in humans. *Behavioral Neuroscience*, *113*(3), 420. Retrieved from http://psycnet.apa.org/psycinfo/1999-11588-002

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209–237. https://doi.org/10.1016/j.bandc.2007.02.007

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Lyte, M. (2011). Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. *BioEssays*, *33*(8), 574–581. https://doi.org/10.1002/bies.201100024

Maalouf, F. T., Klein, C., Clark, L., Sahakian, B. J., LaBarbara, E. J., Versace, A., … Phillips, M. L. (2010). Impaired sustained attention and executive dysfunction: Bipolar disorder versus depression-specific markers of affective disorders. *Neuropsychologia*, *48*(6), 1862–1868. https://doi.org/10.1016/j.neuropsychologia.2010.02.015

Machielsen, W. C., Rombouts, Barkhof, F., Scheltens, & Witter, M. P. (2000). fMRI of visual encoding: reproducibility of activation. *Human Brain Mapping*, *9*, 156–164. Retrieved from http://hdl.handle.net/1871/26274

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research&quest. *Molecular Psychiatry*, *16*(3), 252–264. Retrieved from http://www.nature.com/mp/journal/v16/n3/abs/mp201080a.html

Maniam, J., Antoniadis, C., & Morris, M. J. (2014). Early-Life Stress, HPA Axis Adaptation, and Mechanisms Contributing to Later Health Outcomes. *Frontiers in Endocrinology*, *5*. https://doi.org/10.3389/fendo.2014.00073

Mannie, Z. N., Barnes, J., Bristow, G. C., Harmer, C. J., & Cowen, P. J. (2008). Memory impairment in young women at increased risk of depression: influence of cortisol and 5-HTT genotype. *Psychological Medicine*, *39*(5), 757. https://doi.org/10.1017/S0033291708004248

Mannie, Z. N., Harmer, C. J., & Cowen, P. J. (2007). Increased waking salivary cortisol levels in young people at familial risk of depression. *The American Journal of Psychiatry*, *164*(4), 617–21. https://doi.org/10.1176/appi.ajp.164.4.617

Maras, P. M., & Baram, T. Z. (2012). Sculpting the hippocampus from within: stress, spines, and CRH. *Trends in Neurosciences*, *35*(5), 315–324. https://doi.org/10.1016/j.tins.2012.01.005

Marin, M.-F., Lord, C., Andrews, J., Juster, R.-P., Sindi, S., Arsenault-Lapierre, G., … Lupien, S. J. (2011). Chronic stress, cognitive functioning and mental health. *Neurobiology of Learning and Memory*, *96*(4), 583–595. https://doi.org/10.1016/j.nlm.2011.02.016

Martin, E. I., Ressler, K. J., Binder, E., & Nemeroff, C. B. (2009). The Neurobiology of Anxiety Disorders: Brain Imaging, Genetics, and Psychoneuroendocrinology. *Psychiatric Clinics of North America*, *32*(3), 549–575. https://doi.org/10.1016/j.psc.2009.05.004

Masurier, M. L., Cowen, P. J., & Harmer, C. J. (2006). Emotional bias and waking salivary cortisol in relatives of patients with major depression. *Psychological Medicine*, *37*(3), 403. https://doi.org/10.1017/S0033291706009184

Mather, M., Lighthall, N. R., Nga, L., & Gorlick, M. A. (2010). Sex differences in how stress affects brain activity during face viewing: *NeuroReport*, *21*(14), 933–937. https://doi.org/10.1097/WNR.0b013e32833ddd92

Mayer, E. A. (2011). Gut feelings: the emerging biology of gut–brain communication. *Nature Reviews Neuroscience*, *12*(8), 453–466. https://doi.org/10.1038/nrn3071

McAllister-Williams., R., & Rugg, M. (2002). Effects of repeated cortisol administration on brain potential correlates of episodic memory retrieval. *Psychopharmacology*, *160*(1), 74–83. https://doi.org/10.1007/s00213-001-0938-5

McCabe, C., & Mishor, Z. (2011). Antidepressant medications reduce subcortical–cortical resting-state functional connectivity in healthy volunteers. *NeuroImage*, *57*(4), 1317–1323. https://doi.org/10.1016/j.neuroimage.2011.05.051

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, *338*(3), 171–179. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJM199801153380307

McEwen, B. S. (2003). Mood disorders and allostatic load. *Biological Psychiatry*, *54*(3), 200–207. https://doi.org/10.1016/S0006-3223(03)00177-X

McEwen, B. S. (2007). Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. *Physiological Reviews*, *87*(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and Allostasis-Induced Brain Plasticity. *Annual Review of Medicine*, *62*(1), 431–445. https://doi.org/10.1146/annurev-med-052209-100430

McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior*, *57*(2), 105–111. https://doi.org/10.1016/j.yhbeh.2009.09.011

McGaugh, J. L. (2000). Memory–a century of consolidation. *Science*, *287*(5451), 248–251. Retrieved from http://www.sciencemag.org/content/287/5451/248.short

McGowan, P. O. (2013). Epigenomic Mechanisms of Early Adversity and HPA Dysfunction: Considerations for PTSD Research. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00110

McKlveen, J. M., Myers, B., Flak, J. N., Bundzikova, J., Solomon, M. B., Seroogy, K. B., & Herman, J. P. (2013). Role of Prefrontal Cortex Glucocorticoid Receptors in Stress and Emotion. *Biological Psychiatry*, *74*(9), 672–679. https://doi.org/10.1016/j.biopsych.2013.03.024

Melchior, M., Caspi, A., Milne, B. J., Danese, A., Poulton, R., & Moffitt, T. E. (2007). Work stress precipitates depression and anxiety in young, working women and men. *Psychological Medicine*, *37*(8), 1119–1129. https://doi.org/10.1017/S0033291707000414

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., … Cazaubiel, J.-M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *The British Journal of Nutrition*, *105*(5), 755–64. https://doi.org/10.1017/S0007114510004319

Miller, R., Wankerl, M., Stalder, T., Kirschbaum, C., & Alexander, N. (2012). The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a

meta-analysis. *Molecular Psychiatry*, *18*(9), 1018–1024. https://doi.org/10.1038/mp.2012.124

Min, W., Liu, C., Yang, Y., Sun, X., Zhang, B., Xu, L., & Sun, X. (2012). Alterations in hypothalamic–pituitary–adrenal/thyroid (HPA/HPT) axes correlated with the clinical manifestations of depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(1), 206–211. https://doi.org/10.1016/j.pnpbp.2012.06.017

Mitra, R., & Sapolsky, R. M. (2008). Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. *Proceedings of the National Academy of Sciences*, *105*(14), 5573–5578. https://doi.org/10.1073/pnas.0705615105

Moench, K. M., Maroun, M., Kavushansky, A., & Wellman, C. (2016). Alterations in neuronal morphology in infralimbic cortex predict resistance to fear extinction following acute stress. *Neurobiology of Stress*, *3*, 23–33. https://doi.org/10.1016/j.ynstr.2015.12.002

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy*, *36*(9), 809–848. Retrieved from http://www.sciencedirect.com/science/article/pii/S0005796798000631

Mogg, K., & Bradley, B. P. (2005). Attentional Bias in Generalized Anxiety Disorder Versus Depressive Disorder. *Cognitive Therapy and Research*, *29*(1), 29–45. https://doi.org/10.1007/s10608-005-1646-y

Mogg, K., Bradley, B. P., Dixon, C., Fisher, S., Twelftree, H., & McWilliams, A. (2000). Trait anxiety, defensiveness and selective processing of threat: an investigation using two measures of attentional bias. *Personality and Individual Differences*, *28*(6), 1063–1077. https://doi.org/10.1016/S0191-8869(99)00157-9

Mogg, K., Bradley, B. P., & Hallowell, N. (1994). Attentional bias to threat: Roles of trait anxiety, stressful events, and awareness. *The Quarterly Journal of Experimental Psychology Section A*, *47*(4), 841–864. https://doi.org/10.1080/14640749408401099

Mokhtari, M., Arfken, C., & Boutros, N. (2013). The DEX/CRH test for major depression: A potentially useful diagnostic test. *Psychiatry Research*, *208*(2), 131–139. https://doi.org/10.1016/j.psychres.2012.09.032

Mondelli, V., Ciufolini, S., Murri, M. B., Bonaccorso, S., Di Forti, M., Giordano, A., … others. (2015). Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophrenia Bulletin*, sbv028. Retrieved from https://schizophreniabulletin.oxfordjournals.org/content/early/2015/03/30/schbul.sbv028.full

Mondelli, V., Dazzan, P., Hepgul, N., Di Forti, M., Aas, M., D'Albenzio, A., … Pariante, C. M. (2010). Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment. *Schizophrenia Research*, *116*(2–3), 234–242. https://doi.org/10.1016/j.schres.2009.08.013

Mondelli, V., Pariante, C. M., Navari, S., Aas, M., D'Albenzio, A., Di Forti, M., … Dazzan, P. (2010). Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. *Schizophrenia Research*, *119*(1–3), 75–78. https://doi.org/10.1016/j.schres.2009.12.021

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., … others. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *American Journal of Psychiatry*. Retrieved from http://ajp.psychiatryonline.org/doi/pdf/10.1176/ajp.2006.163.6.1091

Montoya, E. R., Terburg, D., Bos, P. A., & van Honk, J. (2012). Testosterone, cortisol, and serotonin as key regulators of social aggression: A review and theoretical perspective. *Motivation and Emotion*, *36*(1), 65–73. https://doi.org/10.1007/s11031-011-9264-3

Morris, M. C., & Rao, U. (2013). Psychobiology of PTSD in the acute aftermath of trauma: Integrating research on coping, HPA function and sympathetic nervous system activity. *Asian Journal of Psychiatry*, *6*(1), 3–21. https://doi.org/10.1016/j.ajp.2012.07.012

Morris, M. C., Rao, U., & Garber, J. (2012). Cortisol responses to psychosocial stress predict depression trajectories: Social-evaluative threat and prior depressive episodes as moderators. *Journal of Affective Disorders*, *143*(1), 223–230. Retrieved from http://www.sciencedirect.com/science/article/pii/S0165032712004429

Moser, M.-B., & Moser, E. I. (1998). Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway. *HIPPOCAMPUS*, *8*, 608–619. Retrieved from https://www.researchgate.net/profile/May-Britt_Moser/publication/13407030_Moser_MB_Moser_EI_Functional_differentiation_in_the_hippocampus_Hippocampus_8_608-619/links/550b19450cf290bdc111d639.pdf

Moylan, S., Maes, M., Wray, N. R., & Berk, M. (2012). The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Molecular Psychiatry*, *18*(5), 595–606. Retrieved from http://www.nature.com/mp/journal/v18/n5/abs/mp201233a.html

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015). Resting-state functional connectivity in major depressive disorder: A review. *Neuroscience & Biobehavioral Reviews*, *56*, 330–344. https://doi.org/10.1016/j.neubiorev.2015.07.014

Murphy, M. L., & Frodl, T. (2011). Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biology of Mood & Anxiety Disorders*, *1*, 3–3. Retrieved from http://go.galegroup.com/ps/i.do?p=AONE&sw=w&issn=20455380&v=2.1&it=r&id=GALE%7CA270631668&sid=googleScholar&linkaccess=abs

Murphy, S. E., Norbury, R., Godlewska, B. R., Cowen, P. J., Mannie, Z. N., Harmer, C. J., & Munafo, M. R. (2012). The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: a meta-analysis. *Molecular Psychiatry*, *18*(4), 512–520. Retrieved from http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201219a.html

Murphy, S. E., Norbury, R., O'Sullivan, U., Cowen, P. J., & Harmer, C. J. (2009). Effect of a single dose of citalopram on amygdala response to emotional faces. *The British Journal of Psychiatry*, *194*(6), 535–540. https://doi.org/10.1192/bjp.bp.108.056093

Murphy, S. E., Yiend, J., Lester, K. J., Cowen, P. J., & Harmer, C. J. (2009). Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *12*(2), 169–79. https://doi.org/10.1017/S1461145708009164

Murray, R. J., Brosch, T., & Sander, D. (2014). The functional profile of the human amygdala in affective processing: Insights from intracranial recordings. *Cortex*, *60*, 10–33. https://doi.org/10.1016/j.cortex.2014.06.010

Murty, V. P., Ritchey, M., Adcock, R. A., & LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia*, *48*(12), 3459–3469. https://doi.org/10.1016/j.neuropsychologia.2010.07.030

Naber, D., Sand, P., & Heigl, B. (1996). Psychopathological and neuropathological effects of 8-days' corticosteroid treatment. A prospective study. *Psychoneuroendocrinology*, *21*(1), 25–31.

Nater, U. M., Moor, C., Okere, U., Stallkamp, R., Martin, M., Ehlert, U., & Kliegel, M. (2007). Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress. *Psychoneuroendocrinology*, *32*(6), 758–763. https://doi.org/10.1016/j.psyneuen.2007.05.006

Nelson, E. E., McClure, E. B., Monk, C. S., Zarahn, E., Leibenluft, E., Pine, D. S., & Ernst, M. (2003). Developmental differences in neuronal engagement during implicit encoding of emotional faces: an event-related fMRI study. *Journal of Child Psychology and Psychiatry*, *44*(7), 1015–1024. https://doi.org/10.1111/1469-7610.00186

Nelson, H. (1982). The National Adult Reading Test (NART): test manual. NFER-Nelson.

Nemeroff, C. B., Bissette, G., Akil, H., & Fink, M. (1991). Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *The British Journal of Psychiatry*, *158*(1), 59–63. Retrieved from http://bjp.rcpsych.org/content/158/1/59.short

Nemeroff, C. B., & Vale, W. W. (2005). The neurobiology of depression: Inroads to treatment and new drug discovery. *ResearchGate*, *66 Suppl 7*(supplement 7), 5–13. Retrieved from https://www.researchgate.net/publication/7635612_The_neurobiology_of_depression_Inroads_to_treatment_and_new_drug_discovery

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., & Alderson, A. L. (1999). Decreased Memory Performance in Healthy Humans Induced by Stress-Level Cortisol Treatment. *Archives of General Psychiatry*, *56*, 527–533.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*(1), 1–25. https://doi.org/10.1002/hbm.1058

Nijdam, M. J., van Amsterdam, J. G. C., Gersons, B. P. R., & Olff, M. (2015). Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder. *Journal of Affective Disorders*, *184*, 205–208. https://doi.org/10.1016/j.jad.2015.05.058

Nikisch, G., Mathé, A. A., Czernik, A., Thiele, J., Bohner, J., Eap, C. B., … Baumann, P. (2005). Long-term citalopram administration reduces responsiveness of HPA axis in patients with major depression: relationship with S-citalopram concentrations in plasma and cerebrospinal fluid (CSF) and clinical response. *Psychopharmacology*, *181*(4), 751–760. https://doi.org/10.1007/s00213-005-0034-3

Norbury, R., Selvaraj, S., Taylor, M. J., Harmer, C., & Cowen, P. J. (2009). Increased neural response to fear in patients recovered from depression: a 3T functional magnetic resonance imaging study. *Psychological Medicine*, *40*(3), 425. https://doi.org/10.1017/S0033291709990596

Nordholm, D., Krogh, J., Mondelli, V., Dazzan, P., Pariante, C., & Nordentoft, M. (2013). Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *38*(11), 2394–2404. https://doi.org/10.1016/j.psyneuen.2013.06.030

Northoff, G., Wiebking, C., Feinberg, T., & Panksepp, J. (2011). The 'resting-state hypothesis' of major depressive disorder—A translational subcortical–cortical framework for a system disorder. *Neuroscience & Biobehavioral Reviews*, *35*(9), 1929–1945. https://doi.org/10.1016/j.neubiorev.2010.12.007

Oei, N. Y. L., Everaerd, W. T. A. M., Elzinga, B. M., van Well, S., & Bermond, B. (2006). Psychosocial stress impairs working memory at high loads: An association with cortisol levels and memory retrieval. *Stress: The International Journal on the Biology of Stress*, *9*(3), 133–141. https://doi.org/10.1080/10253890600965773

Oei, N. Y. L., Tollenaar, M. S., Spinhoven, P., & Elzinga, B. M. (2009). Hydrocortisone reduces emotional distracter interference in working memory. *Psychoneuroendocrinology*, *34*(9), 1284–1293. https://doi.org/10.1016/j.psyneuen.2009.03.015

Oei, N. Y. L., Veer, I. M., Wolf, O. T., Spinhoven, P., Rombouts, S. A. R. B., & Elzinga, B. M. (2011). Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. *Social Cognitive and Affective Neuroscience*, *7*(4), 403–412. https://doi.org/10.1093/scan/nsr024

Oitzl, M. S., Champagne, D. L., van der Veen, R., & De Kloet, E. R. (2010). Brain development under stress: hypotheses of glucocorticoid actions revisited. *Neuroscience and Biobehavioral Reviews*, *34*(6), 853–66. https://doi.org/10.1016/j.neubiorev.2009.07.006

Ott, V., Friedrich, M., Prilop, S., Lehnert, H., Jauch-Chara, K., Born, J., & Hallschmid, M. (2011). Food anticipation and subsequent food withdrawal increase serum cortisol in healthy men. *Physiology & Behavior*, *103*(5), 594–599. https://doi.org/10.1016/j.physbeh.2011.04.020

Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., & Mohr, D. C. (2005). A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology*, *30*(1), 80–91. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453004001118

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. https://doi.org/10.1002/hbm.20131

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2015). HPA axis genetic variation, pubertal status, and sex interact to predict amygdala and hippocampus responses to negative emotional faces in school-age children. *NeuroImage*, *109*, 1–11. https://doi.org/10.1016/j.neuroimage.2015.01.017

Pannekoek, J. N., van der Werff, S. j. a., Meens, P. H. F., van den Bulk, B. G., Jolles, D. D., Veer, I. M., … Vermeiren, R. R. J. M. (2014). Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naïve clinically depressed adolescents. *Journal of Child Psychology and Psychiatry*, *55*(12), 1317–1327. https://doi.org/10.1111/jcpp.12266

Pannekoek, J. N., Veer, I. M., van Tol, M.-J., van der Werff, S. J. A., Demenescu, L. R., Aleman, A., … van der Wee, N. J. A. (2013). Aberrant limbic and salience network resting-state functional connectivity in panic disorder without comorbidity. *Journal of Affective Disorders*, *145*(1), 29–35. https://doi.org/10.1016/j.jad.2012.07.006

Parent, M. A., Wang, L., Su, J., Netoff, T., & Yuan, L.-L. (2010). Identification of the Hippocampal Input to Medial Prefrontal Cortex In Vitro. *Cerebral Cortex*, *20*(2), 393–403. https://doi.org/10.1093/cercor/bhp108

Pariante, C. M. (2004). Glucocorticoid Receptor Function In Vitro in Patients with Major Depression. *Stress: The International Journal on the Biology of Stress*, *7*(4), 209–219. https://doi.org/10.1080/10253890500069650

Pariante, C. M. (2006). The glucocorticoid receptor: part of the solution or part of the problem? *Journal of Psychopharmacology*, *20*(4 suppl), 79–84. https://doi.org/10.1177/1359786806066063

Pariante, C. M. (2009). Risk Factors for Development of Depression and Psychosis: Glucocorticoid Receptors and Pituitary Implications for Treatment with Antidepressant and Glucocorticoids. *Annals of the New York Academy of Sciences*, *1179*(1), 144–152. https://doi.org/10.1111/j.1749-6632.2009.04978.x

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468. https://doi.org/10.1016/j.tins.2008.06.006

Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological Psychiatry*, *49*(5), 391–404. Retrieved from http://www.sciencedirect.com/science/article/pii/S000632230001088X

Pascual-Le Tallec, L., & Lombès, M. (2005). The Mineralocorticoid Receptor: A Journey Exploring Its Diversity and Specificity of Action. *Molecular Endocrinology*, *19*(9), 2211–2221. https://doi.org/10.1210/me.2005-0089

Patenaude, B., Smith, S. M., Kennedy, D. N., & Jenkinson, M. (2011). A Bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage*, *56*(3), 907–922. https://doi.org/10.1016/j.neuroimage.2011.02.046

Peckham, A. D., McHugh, R. K., & Otto, M. W. (2010). A meta-analysis of the magnitude of biased attention in depression. *Depression and Anxiety*, *27*(12), 1135–42. https://doi.org/10.1002/da.20755

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a'low road'to'many roads' of evaluating biological significance. *Nature Reviews Neuroscience*, *11*(11), 773–783. Retrieved from http://www.nature.com/nrn/journal/v11/n11/abs/nrn2920.html

Pflanz, C. P., Pringle, A., Filippini, N., Warren, M., Gottwald, J., Cowen, P. J., & Harmer, C. J. (2015). Effects of seven-day diazepam administration on resting-state functional connectivity in healthy volunteers: a randomized, double-blind study. *Psychopharmacology*, *232*(12), 2139–2147. https://doi.org/10.1007/s00213-014-3844-3

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional Neuroanatomy of Emotion: A Meta-Analysis of Emotion Activation Studies in PET and fMRI. *NeuroImage*, *16*(2), 331–348. https://doi.org/10.1006/nimg.2002.1087

Philip, N. S., Sweet, L. H., Tyrka, A. R., Price, L. H., Bloom, R. F., & Carpenter, L. L. (2013). Decreased default network connectivity is associated with early life stress in medication-free healthy adults. *European Neuropsychopharmacology*, *23*(1), 24–32. https://doi.org/10.1016/j.euroneuro.2012.10.008

Pishyar, R., Harris, L. M., & Menzies, R. G. (2004). Attentional bias for words and faces in social anxiety. *Anxiety, Stress & Coping*, *17*(1), 23–36. https://doi.org/10.1080/10615800310001601458

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *33*(1), 88–109. https://doi.org/10.1038/sj.npp.1301574

Pivonello, R., Simeoli, C., De Martino, M. C., Cozzolino, A., De Leo, M., Iacuaniello, D., … Colao, A. (2015). Neuropsychiatric disorders in Cushing's syndrome. *Frontiers in Neuroscience*, *9*. https://doi.org/10.3389/fnins.2015.00129

Pizzagalli, D. A. (2010). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*, *36*(1), 183–206. Retrieved from http://www.nature.com/npp/journal/vaop/ncurrent/full/npp2010166a.html

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences*, *17*(5), 230–240. https://doi.org/10.1016/j.tics.2013.03.005

Poppenk, J., & Moscovitch, M. (2011). A Hippocampal Marker of Recollection Memory Ability among Healthy Young Adults: Contributions of Posterior and Anterior Segments. *Neuron*, *72*(6), 931–937. https://doi.org/10.1016/j.neuron.2011.10.014

Porcelli, A. J., Cruz, D., Wenberg, K., Patterson, M. D., Biswal, B. B., & Rypma, B. (2008). The effects of acute stress on human prefrontal working memory systems. *Physiology & Behavior*, *95*(3), 282–289. https://doi.org/10.1016/j.physbeh.2008.04.027

Portella, M. J., Harmer, C. J., Flint, J., Cowen, P., & Goodwin, G. M. (2005). Enhanced early morning salivary cortisol in neuroticism. *The American Journal of Psychiatry*, *162*(4), 807–9. https://doi.org/10.1176/appi.ajp.162.4.807

Postuma, R. B. (2005). Basal Ganglia Functional Connectivity Based on a Meta-Analysis of 126 Positron Emission Tomography and Functional Magnetic Resonance Imaging Publications. *Cerebral Cortex*, *16*(10), 1508–1521. https://doi.org/10.1093/cercor/bhj088

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences*, *16*(1), 61–71. https://doi.org/10.1016/j.tics.2011.12.011

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., … Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences*, *61*(26), 2539–2549.

Putman, P., Hermans, E. J., Koppeschaar, H., van Schijndel, A., & van Honk, J. (2007). A single administration of cortisol acutely reduces preconscious attention for fear in anxious young men. *Psychoneuroendocrinology*, *32*(7), 793–802. https://doi.org/10.1016/j.psyneuen.2007.05.009

Putman, P., Hermans, E. J., & van Honk, J. (2007). Exogenous cortisol shifts a motivated bias from fear to anger in spatial working memory for facial expressions. *Psychoneuroendocrinology*, *32*(1), 14–21. https://doi.org/10.1016/j.psyneuen.2006.09.010

Putman, P., Hermans, E. J., & van Honk, J. (2010). Cortisol administration acutely reduces threat-selective spatial attention in healthy young men. *Physiology & Behavior*, *99*(3), 294–300. https://doi.org/10.1016/j.physbeh.2009.11.006

Putman, P., & Roelofs, K. (2011). Effects of single cortisol administrations on human affect reviewed: Coping with stress through adaptive regulation of automatic cognitive processing. *Psychoneuroendocrinology*, *36*(4), 439–48. https://doi.org/10.1016/j.psyneuen.2010.12.001

Qin, S., Young, C. B., Duan, X., Chen, T., Supekar, K., & Menon, V. (2014). Amygdala Subregional Structure and Intrinsic Functional Connectivity Predicts Individual Differences in Anxiety During Early Childhood. *Biological Psychiatry*, *75*(11), 892–900. https://doi.org/10.1016/j.biopsych.2013.10.006

Quaedflieg, C., van de Ven, V., Meyer, T., Siep, N., Merckelbach, H., & Smeets, T. (2015). Temporal Dynamics of Stress-Induced Alternations of Intrinsic Amygdala Connectivity and Neuroendocrine Levels. Retrieved from http://dx.plos.org/10.1371/journal.pone.0124141

Quaedflieg, C. W. E. M., Schwabe, L., Meyer, T., & Smeets, T. (2013). Time dependent effects of stress prior to encoding on event-related potentials and 24h delayed retrieval. *Psychoneuroendocrinology*, *38*(12), 3057–3069. https://doi.org/10.1016/j.psyneuen.2013.09.002

Radley, J. J., Kabbaj, M., Jacobson, L., Heydendael, W., Yehuda, R., & Herman, J. P. (2011). Stress risk factors and stress-related pathology: Neuroplasticity, epigenetics and endophenotypes. *Stress*, *14*(5), 481–497. https://doi.org/10.3109/10253890.2011.604751

Radley, J. J., Morilak, D., Viau, V., & Campeau, S. (2015). Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2015.06.018

Radley, J. J., Sisti, H. ., Hao, J., Rocher, A. ., McCall, T., Hof, P. ., … Morrison, J. . (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*, *125*(1), 1–6. https://doi.org/10.1016/j.neuroscience.2004.01.006

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682. Retrieved from http://www.pnas.org/content/98/2/676.short

Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola, I., & Goodyear, B. (2014). Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. *Neuropsychiatric Imaging and Stimulation*, *5*, 17. https://doi.org/10.3389/fpsyt.2014.00017

Rao, A. V., Bested, A. C., Beaulne, T. M., Katzman, M. A., Iorio, C., Berardi, J. M., & Logan, A. C. (2009). A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathogens*, *1*(1), 6. https://doi.org/10.1186/1757-4749-1-6

Rao, J. A., Jenkins, L. M., Hymen, E., Feigon, M., Weisenbach, S. L., Zubieta, J.-K., & Langenecker, S. A. (2016). Differential Resting State Connectivity Patterns and Impaired Semantically Cued List Learning Test Performance in Early Course Remitted Major Depressive Disorder. *Journal of the International Neuropsychological Society*, *22*(2), 225–239. https://doi.org/10.1017/S1355617716000011

Reul, J. M. H. M., & De Kloet, E. R. (1985). Two Receptor Systems for Corticosterone in Rat Brain: Microdistribution and Differential Occupation. *Endocrinology*, *117*(6), 2505–2511. https://doi.org/10.1210/endo-117-6-2505

Rhee, S. H., Pothoulakis, C., & Mayer, E. A. (2009). Principles and clinical implications of the brain–gut–enteric microbiota axis. *Nature Reviews Gastroenterology & Hepatology*, *6*(5), 306–314. https://doi.org/10.1038/nrgastro.2009.35

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., … Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and

risk of depression. *JAMA: The Journal of the American Medical Association*, *301*(23), 2462–2471. Retrieved from http://jama.ama-assn.org/content/301/23/2462.short

Ritchey, M., Dolcos, F., Eddington, K. M., Strauman, T. J., & Cabeza, R. (2011). Neural correlates of emotional processing in depression: Changes with cognitive behavioral therapy and predictors of treatment response. *Journal of Psychiatric Research*, *45*(5), 577–587. https://doi.org/10.1016/j.jpsychires.2010.09.007

Robbins, T. W., Gillan, C. M., Smith, D. G., de Wit, S., & Ersche, K. D. (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in Cognitive Sciences*, *16*(1), 81–91. https://doi.org/10.1016/j.tics.2011.11.009

Robinson, J. L., Laird, A. R., Glahn, D. C., Blangero, J., Sanghera, M. K., Pessoa, L., … Fox, P. T. (2012). The functional connectivity of the human caudate: An application of meta-analytic connectivity modeling with behavioral filtering. *NeuroImage*, *60*(1), 117–129. https://doi.org/10.1016/j.neuroimage.2011.12.010

Roelofs, K., Bakvis, P., Hermans, E. J., van Pelt, J., & van Honk, J. (2007). The effects of social stress and cortisol responses on the preconscious selective attention to social threat. *Biological Psychology*, *75*(1), 1–7. https://doi.org/10.1016/j.biopsycho.2006.09.002

Roelofs, K., Elzinga, B. M., & Rotteveel, M. (2005). The effects of stress-induced cortisol responses on approach–avoidance behavior. *Psychoneuroendocrinology*, *30*(7), 665–677. https://doi.org/10.1016/j.psyneuen.2005.02.008

Rohleder, N. (2012). Acute and chronic stress induced changes in sensitivity of peripheral inflammatory pathways to the signals of multiple stress systems – 2011 Curt Richter Award Winner. *Psychoneuroendocrinology*, *37*(3), 307–316. https://doi.org/10.1016/j.psyneuen.2011.12.015

Roiser, J. P., Elliott, R., & Sahakian, B. J. (2011). Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology*, *37*(1), 117–136. Retrieved from http://www.nature.com/npp/journal/v37/n1/abs/npp2011183a.html

Rome, H. P., & Braceland, F. J. (1952). The psychological response to acth, cortisone, hydrocortisone, and related steroid substances. *American Journal of Psychiatry*, *108*(9), 641–651. https://doi.org/10.1176/ajp.108.9.641

Roozendaal, B. (2003). Systems mediating acute glucocorticoid effects on memory consolidation and retrieval. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *27*(8), 1213–1223. https://doi.org/10.1016/j.pnpbp.2003.09.015

Roozendaal, B., Griffith, Q. K., Buranday, J., de Quervain, D. J.-F., & McGaugh, J. L. (2003). The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: Dependence on the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(3), 1328–1333. https://doi.org/10.1073/pnas.0337480100

Roozendaal, B., Okuda, S., de Quervain, D. J.-F., & McGaugh, J. L. (2006). Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience*, *138*(3), 901–910. https://doi.org/10.1016/j.neuroscience.2005.07.049

Rossion, B., Caldara, R., Seghier, M., Schuller, A.-M., Lazeyras, F., & Mayer, E. (2003). A network of occipito- temporal face- sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing. *Brain*, *126*(11), 2381–2395. https://doi.org/10.1093/brain/awg241

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Gotimer, K., … Milham, M. P. (2009). Functional connectivity of the human amygdala using resting state fMRI. *NeuroImage*, *45*(2), 614–626. https://doi.org/10.1016/j.neuroimage.2008.11.030

Royer, S., Sirota, A., Patel, J., & Buzsaki, G. (2010). Distinct Representations and Theta Dynamics in Dorsal and Ventral Hippocampus. *Journal of Neuroscience*, *30*(5), 1777–1787. https://doi.org/10.1523/JNEUROSCI.4681-09.2010

Rusch, B. D., Abercrombie, H. C., Oakes, T. R., Schaefer, S. M., & Davidson, R. J. (2001). Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. *Biological Psychiatry*, *50*(12), 960–964. https://doi.org/10.1016/S0006-3223(01)01248-3

Sabatinelli, D., Frank, D. W., Wanger, T. J., Dhamala, M., Adhikari, B. M., & Li, X. (2014). The timing and directional connectivity of human frontoparietal and ventral visual attention networks in emotional scene perception. *Neuroscience*, *277*, 229–238. https://doi.org/10.1016/j.neuroscience.2014.07.005

Sabatini, E., Penna, S. D., Franciotti, R., Ferretti, A., Zoccolotti, P., Rossini, P. M., … Gainotti, G. (2009). Brain structures activated by overt and covert emotional visual stimuli. *Brain Research Bulletin*, *79*(5), 258–264. https://doi.org/10.1016/j.brainresbull.2009.03.001

Salomons, T. V., Dunlop, K., Kennedy, S. H., Flint, A., Geraci, J., Giacobbe, P., & Downar, J. (2014). Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. *Neuropsychopharmacology*, *39*(2), 488–498. Retrieved from http://www.nature.com/npp/journal/v39/n2/abs/npp2013222a.html

Samuelson, K. W. (2011). Post-traumatic stress disorder and declarative memory functioning: a review. *Dialogues in Clinical Neuroscience*, *13*(3), 346–351. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3182004/

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., … Hen, R. (2003). Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants. *Science*, *301*(5634), 805–809. https://doi.org/10.1126/science.1083328

Sapolsky, R. M. (1994). Individual differences and the stress response. *Seminars in Neuroscience*, *6*(4), 261–269. https://doi.org/10.1006/smns.1994.1033

Sapolsky, R. M. (1995). Social subordinance as a marker of hypercortisolism. *Annals of the New York Academy of Sciences*, *771*(1), 626–639. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.1995.tb44715.x/abstract

Sapolsky, R. M. (1996). Why Stress Is Bad for Your Brain. *Science*, *273*(5276), 749–750. https://doi.org/10.1126/science.273.5276.749

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*(10), 925. Retrieved from http://archpsyc.ama-assn.org/cgi/reprint/57/10/925.pdf

Sapolsky, R. M. (2004). Social Status and Health in Humans and Other Animals. *Annual Review of Anthropology*, *33*, 393–418. Retrieved from http://www.jstor.org/stable/25064859

Sapolsky, R. M., Meaney, M. J., & McEwen, B. S. (1985). The development of the glucocorticoid receptor system in the rat limbic brain. III. Negative-feedback regulation. *Developmental Brain Research*, *18*(1–2), 169–173. https://doi.org/10.1016/0165-3806(85)90261-5

Sarabdjitsingh, R. A., Conway-Campbell, B. L., Leggett, J. D., Waite, E. J., Meijer, O. C., De Kloet, E. R., & Lightman, S. L. (2010). Stress Responsiveness Varies over the Ultradian Glucocorticoid Cycle in a Brain-Region-Specific Manner. *Endocrinology*, *151*(11), 5369–5379. https://doi.org/10.1210/en.2010-0832

Sarabdjitsingh, R. A., Spiga, F., Oitzl, M., Kershaw, Y., Meijer, O. C., Lightman, S. L., & De Kloet, E. R. (2010). Recovery from disrupted ultradian glucocorticoid rhythmicity reveals a dissociation between hormonal and behavioral stress responsiveness. *Journal of Neuroendocrinology*. https://doi.org/10.1111/j.1365-2826.2010.02004.x

Sarrieau, A., O'Donnell, D., Alonso, R., & Meaney, M. J. (1996). Regulation of glucocorticosteroid receptor expression in rat hippocampal cell cultures by nerve growth factor. *Neuroscience Letters*, *206*(2–3), 207–211. https://doi.org/10.1016/S0304-3940(96)12454-X

Sartorius, N., Bedirhan, T., Lecrubier, Y., & Wittchen, H.-U. (1996). Depression comorbid with anxiety: Results from the WHO study on 'Psychological disorders in primary health care.' *The British Journal of Psychiatry*, *168*(Suppl 30), 38–43.

Sasaki, M., Tohyama, K., Matsunaga, S., Nakamura, M., Tomizawa, N., Inoue, T., … Ogawa, A. (2004). MRI identification of dorsal hippocampus homologue in human brain. *Neuroreport*, *15*(14), 2173–2176. Retrieved from http://journals.lww.com/neuroreport/Abstract/2004/10050/MRI_identification_of_dorsal_hippocampus_homologue.5.aspx

Satpute, A. B., Kang, J., Bickart, K. C., Yardley, H., Wager, T. D., & Barrett, L. F. (2015). Involvement of Sensory Regions in Affective Experience: A Meta-Analysis. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01860

Satpute, A. B., Mumford, J. A., Naliboff, B. D., & Poldrack, R. A. (2012). Human anterior and posterior hippocampus respond distinctly to state and trait anxiety. *Emotion*, *12*(1), 58–68. https://doi.org/10.1037/a0026517

Savignac, H. M., Corona, G., Mills, H., Chen, L., Spencer, J. P. E., Tzortzis, G., & Burnet, P. W. J. (2013). Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-d-aspartate receptor subunits and d-serine. *Neurochemistry International*, *63*(8), 756–764. https://doi.org/10.1016/j.neuint.2013.10.006

Savignac, H. M., Couch, Y., Stratford, M., Bannerman, D. M., Tzortzis, G., Anthony, D. C., & Burnet, P. W. J. (2016). Prebiotic administration normalizes lipopolysaccharide (LPS)-induced anxiety and cortical 5-HT2A receptor and IL1-β levels in male mice. *Brain, Behavior, and Immunity*, *52*, 120–131. https://doi.org/10.1016/j.bbi.2015.10.007

Savitz, J., & Drevets, W. C. (2009). Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide. *Neuroscience & Biobehavioral Reviews*, *33*(5), 699–771. https://doi.org/10.1016/j.neubiorev.2009.01.004

Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, *9*(1), 7–24. Retrieved from http://web.mit.edu/wagner/www/papers/SCH_HIP99.pdf

Schalinski, I., Elbert, T., Steudte-Schmiedgen, S., & Kirschbaum, C. (2015). The Cortisol Paradox of Trauma-Related Disorders: Lower Phasic Responses but Higher Tonic Levels of Cortisol Are Associated with Sexual Abuse in Childhood. *PLoS ONE*, *10*(8), e0136921. https://doi.org/10.1371/journal.pone.0136921

Schatzberg, A. F. (2015). Anna-Monika Award Lecture, DGPPN Kongress, 2013: The role of the hypothalamic–pituitary–adrenal (HPA) axis in the pathogenesis of psychotic major depression. *The World Journal of Biological Psychiatry*, *16*(1), 2–11. https://doi.org/10.3109/15622975.2014.916414

Schatzberg, A. F., Keller, J., Tennakoon, L., Lembke, A., Williams, G., Kraemer, F. B., … Murphy, G. M. (2014). HPA axis genetic variation, cortisol and psychosis in major depression. *Molecular Psychiatry*, *19*(2), 220–227. Retrieved from http://www.nature.com/mp/journal/v19/n2/abs/mp2013129a.html

Scheel, M., Ströhle, A., & Bruhn, H. (2010). Effects of short-term stress-like cortisol on cerebral metabolism: A proton magnetic resonance spectroscopy study at 3.0 T. *Journal of Psychiatric Research*, *44*(8), 521–526. https://doi.org/10.1016/j.jpsychires.2009.11.010

Schipper, P., Lopresto, D., Reintjes, R. J., Joosten, J., Henckens, M. J., Kozicz, T., & Homberg, J. R. (2015). Improved Stress Control in Serotonin Transporter Knockout Rats: Involvement of the Prefrontal Cortex and Dorsal Raphe Nucleus. *ACS Chemical Neuroscience*, *6*(7), 1143–1150. https://doi.org/10.1021/acschemneuro.5b00126

Schlotz, W., Yim, I. S., Zoccola, P. M., Jansen, L., & Schulz, P. (2011). The perceived stress reactivity scale: Measurement invariance, stability, and validity in three countries. *Psychological Assessment*, *23*(1), 80–94. https://doi.org/10.1037/a0021148

Schmaal, L., Marquand, A. F., Rhebergen, D., van Tol, M.-J., Ruhé, H. G., van der Wee, N. J. A., … Penninx, B. W. J. H. (2015). Predicting the Naturalistic Course of Major Depressive Disorder Using Clinical and Multimodal Neuroimaging Information: A Multivariate Pattern Recognition Study. *Biological Psychiatry*, *78*(4), 278–286. https://doi.org/10.1016/j.biopsych.2014.11.018

Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., … Hibar, D. P. (2015). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2015.69

Schönfeld, P., Ackermann, K., & Schwabe, L. (2014). Remembering under stress: Different roles of autonomic arousal and glucocorticoids in memory retrieval. *Psychoneuroendocrinology*, *39*, 249–256. https://doi.org/10.1016/j.psyneuen.2013.09.020

Schoofs, D., Preuß, D., & Wolf, O. T. (2008). Psychosocial stress induces working memory impairments in an n-back paradigm. *Psychoneuroendocrinology*, *33*(5), 643–653. https://doi.org/10.1016/j.psyneuen.2008.02.004

Schroeder, R. W., Twumasi-Ankrah, P., Baade, L. E., & Marshall, P. S. (2012). Reliable Digit Span A Systematic Review and Cross-Validation Study. *Assessment*, *19*(1), 21–30. https://doi.org/10.1177/1073191111428764

Schultebraucks, K., Wingenfeld, K., Heimes, J., Quinkler, M., & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison's disease). *Psychoneuroendocrinology*, *55*, 1–7. https://doi.org/10.1016/j.psyneuen.2015.01.025

Schwabe, L., Bohbot, V. D., & Wolf, O. T. (2012). Prenatal stress changes learning strategies in adulthood. *Hippocampus*, *22*(11), 2136–2143. https://doi.org/10.1002/hipo.22034

Schwabe, L., Dalm, S., Schächinger, H., & Oitzl, M. S. (2008). Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. *Neurobiology of Learning and Memory*, *90*(3), 495–503. https://doi.org/10.1016/j.nlm.2008.07.015

Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews*, *36*(7), 1740–1749. https://doi.org/10.1016/j.neubiorev.2011.07.002

Schwabe, L., Oitzl, M. S., Philippsen, C., Richter, S., Bohringer, A., Wippich, W., & Schachinger, H. (2007). Stress modulates the use of spatial versus stimulus-response learning strategies in humans. *Learning & Memory*, *14*(1–2), 109–116. https://doi.org/10.1101/lm.435807

Schwabe, L., Schächinger, H., De Kloet, E. R., & Oitzl, M. S. (2010). Stress impairs spatial but not early stimulus–response learning. *Behavioural Brain Research*, *213*(1), 50–55. https://doi.org/10.1016/j.bbr.2010.04.029

Schwabe, L., & Wolf, O. T. (2011). Stress-induced modulation of instrumental behavior: From goal-directed to habitual control of action. *Behavioural Brain Research*, *219*(2), 321–328. https://doi.org/10.1016/j.bbr.2010.12.038

Schwabe, L., & Wolf, O. T. (2012). Stress Modulates the Engagement of Multiple Memory Systems in Classification Learning. *Journal of Neuroscience*, *32*(32), 11042–11049. https://doi.org/10.1523/JNEUROSCI.1484-12.2012

Schwabe, L., & Wolf, O. T. (2013). Stress and multiple memory systems: from 'thinking' to 'doing'. *Trends in Cognitive Sciences*, *17*(2), 60–68. https://doi.org/10.1016/j.tics.2012.12.001

Schwabe, L., Wolf, O. T., & Oitzl, M. S. (2010). Memory formation under stress: Quantity and quality. *Neuroscience & Biobehavioral Reviews*, *34*(4), 584–591. https://doi.org/10.1016/j.neubiorev.2009.11.015

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *32*(4), 811–830. https://doi.org/10.1016/j.neubiorev.2007.12.002

Sharvit, A., Segal, M., Kehat, O., Stork, O., & Richter-Levin, G. (2015). Differential modulation of synaptic plasticity and local circuit activity in the dentate gyrus and CA1 regions of the rat

hippocampus by corticosterone. *Stress*, *18*(3), 319–327. https://doi.org/10.3109/10253890.2015.1023789

Sheline, Y. I. (2000). 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. *Biological Psychiatry*, *48*(8), 791–800. Retrieved from http://www.sciencedirect.com/science/article/pii/S000632230000994X

Sheline, Y. I. (2003). Neuroimaging studies of mood disorder effects on the brain. *Biological Psychiatry*, *54*(3), 338–352. https://doi.org/10.1016/S0006-3223(03)00347-0

Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, a Z., & Mintun, M. a. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry*, *50*(9), 651–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11704071

Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Activity in Both Hippocampus and Perirhinal Cortex Predicts the Memory Strength of Subsequently Remembered Information. *Neuron*, *59*(4), 547–553. https://doi.org/10.1016/j.neuron.2008.07.022

Shvil, E., Rusch, H. L., Sullivan, G. M., & Neria, Y. (2013). Neural, Psychophysiological, and Behavioral Markers of Fear Processing in PTSD: A Review of the Literature. *Current Psychiatry Reports*, *15*(5). https://doi.org/10.1007/s11920-013-0358-3

Siegle, G., Carter, C., & Thase, M. (2006). Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. *American Journal of Psychiatry*, *163*(4), 735–738. Retrieved from http://journals.psychiatryonline.org/article.aspx?Volume=163&page=735&journalID=13

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., … others. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, *106*(31), 13040–13045. Retrieved from http://www.pnas.org/content/106/31/13040.short

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, *Supplement 1*, S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061

Smoller, J. W. (2016). The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology*, *41*(1), 297–319. https://doi.org/10.1038/npp.2015.266

Soares, J. M., Sampaio, A., Ferreira, L. M., Santos, N. C., Marques, P., Marques, F., … Sousa, N. (2013). Stress Impact on Resting State Brain Networks. *PLoS ONE*, *8*(6), e66500. https://doi.org/10.1371/journal.pone.0066500

Soares, J. M., Sampaio, A., Marques, P., Ferreira, L. M., Santos, N. C., Marques, F., … Sousa, N. (2013). Plasticity of resting state brain networks in recovery from stress. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00919

Sonino, N., & Fava, G. A. (1998). Psychological aspects of endocrine disease. *Clinical Endocrinology*, *49*(1), 1–7. Retrieved from http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2265.1998.00528.x/full

Sonino, N., Fava, G. A., Raffi, A. R., Boscaro, M., & Fallo, F. (1998). Clinical Correlates of Major Depression in Cushing's Disease. *Psychopathology*, *31*, 302–306.

Sonino, Nicoletta, Fava, Giovanni A., Belluardo, P., Girelli, M. E., & Boscaro, M. (1993). Course of Depression in Cushing's Syndrome: Response to Treatment and Comparison with Graves' Disease. *Hormone Research*, *39*, 202–206.

Spielberger, C., Gorsuch, R., & Lushene, R. (1970). *Manual for the State-Trait Anxiety Inventory (STAI)*. Palo Alto, CA: Consulting Psychologists Press.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). THE MEDIAL TEMPORAL LOBE*. *Annual Review of Neuroscience*, *27*(1), 279–306. https://doi.org/10.1146/annurev.neuro.27.070203.144130

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*(5026), 1380–1386. https://doi.org/10.1126/science.1896849

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574. https://doi.org/10.1073/pnas.0800005105

Sripada, R. K., King, A. P., Welsh, R. C., Garfinkel, S. N., Wang, X., Sripada, C. S., & Liberzon, I. (2012). Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium Between Salience and Default Mode Brain Networks. *Psychosomatic Medicine*, *74*(9), 904–911. https://doi.org/10.1097/PSY.0b013e318273bf33

Sripada, R. K., Swain, J. E., Evans, G. W., Welsh, R. C., & Liberzon, I. (2014). Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. *Neuropsychopharmacology*, *39*(9), 2244–2251. Retrieved from http://www.nature.com/npp/journal/v39/n9/abs/npp201475a.html

Stanton, S. J., Wirth, M. M., Waugh, C. E., & Schultheiss, O. C. (2009). Endogenous testosterone levels are associated with amygdala and ventromedial prefrontal cortex responses to anger faces in men but not women. *Biological Psychology*, *81*(2), 118–122. https://doi.org/10.1016/j.biopsycho.2009.03.004

Starkman, M. N. (2013). Neuropsychiatric Findings in Cushing Syndrome and Exogenous Glucocorticoid Administration. *Endocrinology and Metabolism Clinics of North America*, *42*(3), 477–488. https://doi.org/10.1016/j.ecl.2013.05.010

Starkman, M. N., Gebarski, S. S., Berent, S., & Schteingart, D. E. (1992). Hippocampal Formation Volume, Memory Dysfunction, and Cortisol Levels in Patients with Cushing's Syndrome. *Biological Psychiatry*, *32*, 756–765.

Starkman, M. N., Giordani, B., Berent, S., Schork, M. A., & Schteingart, D. E. (2001). Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. *Psychosomatic Medicine*, *63*(6), 985–993. Retrieved from http://journals.lww.com/psychosomaticmedicine/Abstract/2001/11000/Elevated_Cortisol_Levels_in_Cushing_s_Disease_Are.18.aspx

Starkman, M. N., Giordani, B., Gebarski, S. S., & Schteingart, D. E. (2007). Improvement in mood and ideation associated with increase in right caudate volume. *Journal of Affective Disorders*, *101*(1–3), 139–147. https://doi.org/10.1016/j.jad.2006.11.007

Starkman, M. N., & Schteingart, D. E. (1981). Neuropsychiatric manifestations of patients with Cushing's syndrome: relationship to cortisol and adrenocorticotropic hormone levels. *Archives of Internal Medicine*, *141*(2), 215–219. Retrieved from http://archinte.jamanetwork.com/article.aspx?articleid=600731

Starkman, M. N., Schteingart, D. E., & Schork, M. A. (1986). Cushing's Syndrome After Treatment: Changes in Cortisol and ACTH Levels, and Amelioration of the Depressive Syndrome. *Psychiatry Research*, *19*, 177–188.

Starr, L. R., Hammen, C., Conway, C. C., Raposa, E., & Brennan, P. A. (2014). Sensitizing effect of early adversity on depressive reactions to later proximal stress: Moderation by polymorphisms in serotonin transporter and corticotropin releasing hormone receptor genes in a 20-year longitudinal study. *Development and Psychopathology*, *26*(4pt2), 1241–1254. https://doi.org/10.1017/S0954579414000996

Stauble, M. R., Thompson, L. A., & Morgan, G. (2013). Increases in cortisol are positively associated with gains in encoding and maintenance working memory performance in young men. *Stress*, *16*(4), 402–410. https://doi.org/10.3109/10253890.2013.780236

Staufenbiel, S. M., Penninx, B. W. J. H., Spijker, A. T., Elzinga, B. M., & van Rossum, E. F. C. (2013). Hair cortisol, stress exposure, and mental health in humans: A systematic review. *Psychoneuroendocrinology*, *38*(8), 1220–1235. https://doi.org/10.1016/j.psyneuen.2012.11.015

Staugaard, S. R. (2010). Threatening faces and social anxiety: A literature review. *Clinical Psychology Review*, *30*(6), 669–690. https://doi.org/10.1016/j.cpr.2010.05.001

Stein, M. B. (2002). Increased Amygdala Activation to Angry And Contemptuous Faces in Generalized Social Phobia.

Steinmetz, K. R. M., Anderson, A. J., Brasher, K. L., & Brehmer, T. S. (2015). Cortisol and stimulus-induced arousal level differentially impact memory for items and backgrounds. *Cognition and Emotion*, *0*(0), 1–14. https://doi.org/10.1080/02699931.2015.1111197

Sterner, E. Y., & Kalynchuk, L. E. (2010). Behavioral and neurobiological consequences of prolonged glucocorticoid exposure in rats: Relevance to depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(5), 777–790. https://doi.org/10.1016/j.pnpbp.2010.03.005

Stetler, C., & Miller, G. E. (2005). Blunted Cortisol Response to Awakening in Mild to Moderate Depression: Regulatory Influences of Sleep Patterns and Social Contacts. *Journal of Abnormal Psychology*, *114*(4), 697–705. https://doi.org/10.1037/0021-843X.114.4.697

Stetler, C., & Miller, G. E. (2011). Depression and Hypothalamic-Pituitary-Adrenal Activation: A Quantitative Summary of Four Decades of Research: *Psychosomatic Medicine*, *73*(2), 114–126. https://doi.org/10.1097/PSY.0b013e31820ad12b

Steudte, S., Kirschbaum, C., Gao, W., Alexander, N., Schönfeld, S., Hoyer, J., & Stalder, T. (2013). Hair Cortisol as a Biomarker of Traumatization in Healthy Individuals and Posttraumatic Stress Disorder Patients. *Biological Psychiatry*, *74*(9), 639–646. https://doi.org/10.1016/j.biopsych.2013.03.011

Straub, R. H., Buttgereit, F., & Cutolo, M. (2010). Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases - a role for misguided energy regulation. *Clinical and Experimental Rheumatology*, *29*(5 Suppl 68), S23-31. Retrieved from http://europepmc.org/abstract/med/22018180

Strauss, M. M., Makris, N., Aharon, I., Vangel, M. G., Goodman, J., Kennedy, D. N., … Breiter, H. C. (2005). fMRI of sensitization to angry faces. *NeuroImage*, *26*(2), 389–413. https://doi.org/10.1016/j.neuroimage.2005.01.053

Strickland, P. L. (2002). Bio-social origins of depression in the community: Interactions between social adversity, cortisol and serotonin neurotransmission. *The British Journal of Psychiatry*, *180*(2), 168–173. https://doi.org/10.1192/bjp.180.2.168

Sudheimer, K. D., Abelson, J. L., Taylor, S. F., Martis, B., Welsh, R. C., Warner, C., … Liberzon, I. (2012). Exogenous Glucocorticoids Decrease Subgenual Cingulate Activity Evoked by Sadness. *Neuropsychopharmacology*, *38*(5), 826–845. Retrieved from http://www.nature.com/npp/journal/v38/n5/abs/npp2012249a.html

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.-N., … Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of Physiology*, *558*(Pt 1), 263–275. Retrieved from http://discovery.ucl.ac.uk/176047/

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry*, *157*(10), 1552–1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Surguladze, S. A., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., … Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry*, *57*(3), 201–209. https://doi.org/10.1016/j.biopsych.2004.10.028

Surguladze, S. A., El-Hage, W., Dalgleish, T., Radua, J., Gohier, B., & Phillips, M. L. (2010). Depression is associated with increased sensitivity to signals of disgust: A functional

magnetic resonance imaging study. *Journal of Psychiatric Research*, *44*(14), 894–902. https://doi.org/10.1016/j.jpsychires.2010.02.010

Surguladze, S. A., Young, A. W., Senior, C., Brébion, G., Travis, M. J., & Phillips, M. L. (2004). Recognition Accuracy and Response Bias to Happy and Sad Facial Expressions in Patients With Major Depression. *Neuropsychology*, *18*(2), 212–218. https://doi.org/10.1037/0894-4105.18.2.212

Suri, S., Mackay, C. E., Kelly, M. E., Germuska, M., Tunbridge, E. M., Frisoni, G. B., … Filippini, N. (2014). Reduced cerebrovascular reactivity in young adults carrying the APOE ε4 allele. *Alzheimer's & Dementia*. https://doi.org/10.1016/j.jalz.2014.05.1755

Suzuki, A., Poon, L., Kumari, V., & Cleare, A. J. (2015). Fear Biases in Emotional Face Processing Following Childhood Trauma as a Marker of Resilience and Vulnerability to Depression. *Child Maltreatment*, *20*(4), 240–250. https://doi.org/10.1177/1077559515600781

Symonds, C. S., McKie, S., Elliott, R., William Deakin, J. F., & Anderson, I. M. (2012). Detection of the acute effects of hydrocortisone in the hippocampus using pharmacological fMRI. *European Neuropsychopharmacology*, *22*(12), 867–874. https://doi.org/10.1016/j.euroneuro.2012.03.008

Szot, P., White, S. S., Greenup, J. L., Leverenz, J. B., Peskind, E. R., & Raskind, M. A. (2006). Compensatory Changes in the Noradrenergic Nervous System in the Locus Ceruleus and Hippocampus of Postmortem Subjects with Alzheimer's Disease and Dementia with Lewy Bodies. *The Journal of Neuroscience*, *26*(2), 467–478. https://doi.org/10.1523/JNEUROSCI.4265-05.2006

Terburg, D., Morgan, B., & van Honk, J. (2009). The testosterone–cortisol ratio: A hormonal marker for proneness to social aggression. *International Journal of Law and Psychiatry*, *32*(4), 216–223. https://doi.org/10.1016/j.ijlp.2009.04.008

Tessner, K. D., Walker, E. F., Hochman, K., & Hamann, S. (2006). Cortisol responses of healthy volunteers undergoing magnetic resonance imaging. *Human Brain Mapping*, *27*(11), 889–895. https://doi.org/10.1002/hbm.20229

The Boston Collaborative Drug Surveillance Program. (1972). Acute adverse reactions to prednisone in relation to dosage. *Clinical Pharmacology and Therapeutics*, *13*(5), 694–698.

Thomason, M. E., Hamilton, J. P., & Gotlib, I. H. (2011). Stress-induced activation of the HPA axis predicts connectivity between subgenual cingulate and salience network during rest in adolescents: Intrinsic brain connectivity and HPA stress response in adolescents. *Journal of Child Psychology and Psychiatry*, *52*(10), 1026–1034. https://doi.org/10.1111/j.1469-7610.2011.02422.x

Thomson, F., & Craighead, M. (2007). Innovative Approaches for the Treatment of Depression: Targeting the HPA Axis. *Neurochemical Research*, *33*(4), 691–707. https://doi.org/10.1007/s11064-007-9518-3

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., … Mayer, E. a. (2013). Consumption of Fermented Milk Product with Probiotic Modulates Brain Activity. *Gastroenterology*, *144*(7), 1394–1401.e4. https://doi.org/10.1053/j.gastro.2013.02.043

Toffanin, T., Nifosì, F., Follador, H., Passamani, A., Zonta, F., Ferri, G., … Perini, G. I. (2011). Volumetric MRI analysis of hippocampal subregions in Cushing's disease: A model for glucocorticoid neural modulation. *European Psychiatry*, *26*(1), 64–67. https://doi.org/10.1016/j.eurpsy.2010.09.003

Toki, S., Okamoto, Y., Onoda, K., Matsumoto, T., Yoshimura, S., Kunisato, Y., … Yamawaki, S. (2014). Hippocampal activation during associative encoding of word pairs and its relation to symptomatic improvement in depression: A functional and volumetric MRI study. *Journal of Affective Disorders*, *152–154*, 462–467. https://doi.org/10.1016/j.jad.2013.07.021

Tops, M. (2003). Acute cortisol effects on immediate free recall and recognition of nouns depend on stimulus valence.

Tran, U. S., Lamplmayr, E., Pintzinger, N. M., & Pfabigan, D. M. (2013). Happy and angry faces: Subclinical levels of anxiety are differentially related to attentional biases in men and women. *Journal of Research in Personality*, *47*(4), 390–397. https://doi.org/10.1016/j.jrp.2013.03.007

Travis, S. G., Coupland, N. J., Hegadoren, K., Silverstone, P. H., Huang, Y., Carter, R., … Malykhin, N. V. (2016). Effects of cortisol on hippocampal subfields volumes and memory performance in healthy control subjects and patients with major depressive disorder. *Journal of Affective Disorders*, *201*, 34–41. https://doi.org/10.1016/j.jad.2016.04.049

Tyrka, A. R., Price, L. H., Gelernter, J., Schepker, C., Anderson, G. M., & Carpenter, L. L. (2009). Interaction of Childhood Maltreatment with the Corticotropin-Releasing Hormone Receptor Gene: Effects on Hypothalamic-Pituitary-Adrenal Axis Reactivity. *Biological Psychiatry*, *66*(7), 681–685. https://doi.org/10.1016/j.biopsych.2009.05.012

Urry, H. L. (2006). Amygdala and Ventromedial Prefrontal Cortex Are Inversely Coupled during Regulation of Negative Affect and Predict the Diurnal Pattern of Cortisol Secretion among Older Adults. *Journal of Neuroscience*, *26*(16), 4415–4425. https://doi.org/10.1523/JNEUROSCI.3215-05.2006

Vaisvaser, S., Lin, T., Admon, R., Podlipsky, I., Greenman, Y., Stern, N., … Hendler, T. (2013). Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00313

Vakil, E., Greenstein, Y., & Blachstein, H. (2010). Normative Data for Composite Scores for Children and Adults Derived from the Rey Auditory Verbal Learning Test. *The Clinical Neuropsychologist*, *24*(4), 662–677. https://doi.org/10.1080/13854040903493522

Valentino, R. J., Foote, S. L., & Page, M. E. (1993). The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. *Annals of the New York Academy of Sciences*, *697*, 173–188.

Van den Stock, J., Tamietto, M., Sorger, B., Pichon, S., Grezes, J., & de Gelder, B. (2011). Cortico-subcortical visual, somatosensory, and motor activations for perceiving dynamic whole-body emotional expressions with and without striate cortex (V1). *Proceedings of the National Academy of Sciences*, *108*(39), 16188–16193. https://doi.org/10.1073/pnas.1107214108

Van Honk, J., Kessels, R. P. C., Putman, P., Jager, G., Koppeschaar, H. P. F., & Postma, A. (2003). Attentionally modulated effects of cortisol and mood on memory for emotional faces in healthy young males. *Psychoneuroendocrinology*, *28*(7), 941–948. https://doi.org/10.1016/S0306-4530(02)00116-6

van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernández, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *NeuroImage*, *53*(1), 348–354. https://doi.org/10.1016/j.neuroimage.2010.05.070

van Santen, A., Vreeburg, S. A., Van der Does, A. J. W., Spinhoven, P., Zitman, F. G., & Penninx, B. W. J. H. (2011). Psychological traits and the cortisol awakening response: Results from the Netherlands Study of Depression and Anxiety. *Psychoneuroendocrinology*, *36*(2), 240–248. https://doi.org/10.1016/j.psyneuen.2010.07.014

van Stegeren. (2009). Imaging stress effects on memory: a review of neuroimaging studies.

van Tol, M.-J., Veer, I. M., van der Wee, N. J. A., Aleman, A., van Buchem, M. A., Rombouts, S. A. R. B., … Johnstone, T. (2013). Whole-brain functional connectivity during emotional word classification in medication-free Major Depressive Disorder: Abnormal salience circuitry and relations to positive emotionality. *NeuroImage: Clinical*, *2*, 790–796. https://doi.org/10.1016/j.nicl.2013.05.012

Vedhara, K., Miles, J., Bennett, P., Plummer, S., Tallon, D., Brooks, E., … others. (2003). An investigation into the relationship between salivary cortisol, stress, anxiety and depression. *Biological Psychology*, *62*(2), 89–96. Retrieved from http://www.sciencedirect.com/science/article/pii/S030105110200128X

Veen, G., van Vliet, I. M., DeRijk, R. H., Giltay, E. J., van Pelt, J., & Zitman, F. G. (2011). Basal cortisol levels in relation to dimensions and DSM-IV categories of depression and anxiety. *Psychiatry Research*, *185*(1–2), 121–128. https://doi.org/10.1016/j.psychres.2009.07.013

Veer, I. M., Beckmann, C., Van Tol, M.-J., Ferrarini, L., Milles, J., Veltman, D., … Rombouts, S. A. R. (2010). Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Frontiers in Systems Neuroscience*, *4*, 41. https://doi.org/10.3389/fnsys.2010.00041

Veer, I. M., Oei, N. Y. L., Spinhoven, P., van Buchem, M. A., Elzinga, B. M., & Rombouts, S. A. R. B. (2011). Beyond acute social stress: Increased functional connectivity between amygdala and cortical midline structures. *NeuroImage*, *57*(4), 1534–1541. https://doi.org/10.1016/j.neuroimage.2011.05.074

Veer, I. M., Oei, N. Y. L., Spinhoven, P., van Buchem, M. A., Elzinga, B. M., & Rombouts, S. A. R. B. (2012). Endogenous cortisol is associated with functional connectivity between the amygdala and medial prefrontal cortex. *Psychoneuroendocrinology*, *37*(7), 1039–1047. https://doi.org/10.1016/j.psyneuen.2011.12.001

Victor, T. A., Furey, M. L., Fromm, S. J., Öhman, A., & Drevets, W. C. (2010). Relationship of Emotional Processing to Masked Faces in the Amygdala to Mood State and Treatment in Major Depressive Disorder. *Archives of General Psychiatry*, *67*(11), 1128–1138. https://doi.org/10.1001/archgenpsychiatry.2010.144

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *The American Journal of Psychiatry*, *161*(11), 1957–1966. https://doi.org/10.1176/appi.ajp.161.11.1957

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology*, *100*(6), 3328–3342. https://doi.org/10.1152/jn.90355.2008

Vogel, S., Klumpers, F., Kroes, M. C. W., Oplaat, K. T., Krugers, H. J., Oitzl, M. S., … Fernández, G. (2015). A Stress-Induced Shift From Trace to Delay Conditioning Depends on the Mineralocorticoid Receptor. *Biological Psychiatry*, *78*(12), 830–839. https://doi.org/10.1016/j.biopsych.2015.02.014

Vogel, S., Klumpers, F., Krugers, H. J., Fang, Z., Oplaat, K. T., Oitzl, M. S., … Fernández, G. (2014). Blocking the Mineralocorticoid Receptor in Humans Prevents the Stress-Induced Enhancement of Centromedial Amygdala Connectivity with the Dorsal Striatum. *Neuropsychopharmacology*. Retrieved from http://www.nature.com/npp/journal/vaop/ncurrent/full/npp2014271a.html

von Zerssen, D., Strian, F., & Schwarz, D. (1974). Evaluation of depressive states, especially in longitudinal studies. In *Psychological Measurements in Psychopharmacology* (Pichot P Basel, pp. 189–202). Switzerland: Karger.

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., DeRijk, R. H., Verhagen, J. C., van Dyck, R., … Penninx, B. W. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Archives of General Psychiatry*, *66*(6), 617–626. Retrieved from http://archpsyc.jamanetwork.com/article.aspx?articleid=210288&resultclick=1

Vrshek-Schallhorn, S., Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2013). The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. *Psychological Medicine*, *43*(3), 483–493. https://doi.org/10.1017/S0033291712001213

Vyas, A., Mitra, R., Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *The Journal of Neuroscience*, *22*(15), 6810–6818. Retrieved from http://www.jneurosci.org/content/22/15/6810.short

Vythilingam, M., Vermetten, E., Anderson, G. M., Luckenbaugh, D., Anderson, E. R., Snow, J., … Bremner, J. D. (2004). Hippocampal volume, memory, and cortisol status in major

depressive disorder: effects of treatment. *Biological Psychiatry*, *56*(2), 101–112. https://doi.org/10.1016/j.biopsych.2004.04.002

Wada, K., Yamada, N., Sato, T., Suzuki, H., Miki, M., Lee, Y., … Kuroda, S. (2001). Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. *Psychosomatics*, *42*(6), 461–466. Retrieved from http://www.sciencedirect.com/science/article/pii/S0033318201704525

Wagner, K. V., Marinescu, D., Hartmann, J., Wang, X.-D., Labermaier, C., Scharf, S. H., … Schmidt, M. V. (2012). Differences in FKBP51 Regulation Following Chronic Social Defeat Stress Correlate with Individual Stress Sensitivity: Influence of Paroxetine Treatment. *Neuropsychopharmacology*, *37*(13), 2797–2808. https://doi.org/10.1038/npp.2012.150

Walker, J. J., Terry, J. R., & Lightman, S. L. (2010). Origin of ultradian pulsatility in the hypothalamic-pituitary-adrenal axis. *Proceedings of the Royal Society B: Biological Sciences*, *277*(1688), 1627–1633. https://doi.org/10.1098/rspb.2009.2148

Walsh, A. E., & Harmer, C. J. (2015). The cognitive neuropsychological model of antidepressant response. *Current Opinion in Psychology*, *4*, 124–130. https://doi.org/10.1016/j.copsyc.2014.12.022

Wang, Z.-J., Zhang, X.-Q., Cui, X.-Y., Cui, S.-Y., Yu, B., Sheng, Z.-F., … Zhang, Y.-H. (2015). Glucocorticoid receptors in the locus coeruleus mediate sleep disorders caused by repeated corticosterone treatment. *Scientific Reports*, *5*, 9442. https://doi.org/10.1038/srep09442

Wankerl, M., Zyriax, B.-C., Bondy, B., Hinkelmann, K., Windler, E., & Otte, C. (2010). Serotonin transporter gene-linked polymorphic region (5-HTTLPR) and diurnal cortisol: A sex by genotype interaction. *Biological Psychology*, *85*(2), 344–346. https://doi.org/10.1016/j.biopsycho.2010.07.007

Wardenaar, K. J., Vreeburg, S. A., van Veen, T., Giltay, E. J., Veen, G., Penninx, B. W. J. H., & Zitman, F. G. (2011). Dimensions of Depression and Anxiety and the Hypothalamo-Pituitary-Adrenal Axis. *Biological Psychiatry*, *69*(4), 366–373. https://doi.org/10.1016/j.biopsych.2010.09.005

Warren, M. B., Pringle, A., & Harmer, C. J. (2015a). A neurocognitive model for understanding treatment action in depression. *Phil. Trans. R. Soc. B*, *370*(1677), 20140213. https://doi.org/10.1098/rstb.2014.0213

Warren, M. B., Pringle, A., & Harmer, C. J. (2015b). A neurocognitive model for understanding treatment action in depression. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *370*(1677), 20140213. https://doi.org/10.1098/rstb.2014.0213

Wasserman, D., Wasserman, J., & Sokolowski, M. (2010). Genetics of HPA-axis, depression and suicidality. *European Psychiatry*, *25*(5), 278–280. https://doi.org/10.1016/j.eurpsy.2009.12.016

Watson, D., Clark, L., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the Positive and Negative Affect Schedule scales. *Journal of Personality and Social Psychology*, *54*, 1063–1070.

Watzka, M., Beyenburg, S., Blümcke, I., Elger, C. E., Bidlingmaier, F., & Stoffel-Wagner, B. (2000). Expression of mineralocorticoid and glucocorticoid receptor mRNA in the human hippocampus. *Neuroscience Letters*, *290*(2), 121–124. https://doi.org/10.1016/S0304-3940(00)01325-2

Watzka, M., Bidlingmaier, F., Beyenburg, S., Henke, R. T., Clusmann, H., Elger, C. E., … Stoffel-Wagner, B. (2000). Corticosteroid receptor mRNA expression in the brains of patients with epilepsy. *Steroids*, *65*(12), 895–901. https://doi.org/10.1016/S0039-128X(00)00205-1

Wechsler, D. (1981). *Wechler adult intelligence scale-revised (WAIS-R)*. Psychological Corporation.

Weitzman, E. D., Fukushima, D., Nogeire, C., Roffwarg, H., Gallagher, T. F., & Hellman, L. (1971). Twenty-four Hour Pattern of the Episodic Secretion of Cortisol in Normal

Subjects. *The Journal of Clinical Endocrinology & Metabolism*, *33*(1), 14–22. https://doi.org/10.1210/jcem-33-1-14

Werner, N. S., Meindl, T., Materne, J., Engel, R. R., Huber, D., Riedel, M., … Hennig-Fast, K. (2009). Functional MRI study of memory-related brain regions in patients with depressive disorder. *Journal of Affective Disorders*, *119*(1–3), 124–131. https://doi.org/10.1016/j.jad.2009.03.003

Whalen, P. J. (2001). A Functional MRI Study of Human Amygdala Responses to Facial Expressions of Fear Versus Anger.

Whalen, P. J. (2004). Human Amygdala Responsivity to Masked Fearful Eye Whites. *Science*, *306*(5704), 2061–2061. https://doi.org/10.1126/science.1103617

Whalen, P. J., Shin, L. M., McInerney, S. C., Fischer, H., Wright, C. I., & Rauch, S. L. (2001). A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion*, *1*(1), 70–83. https://doi.org/10.1037/1528-3542.1.1.70

Willeumier, K., Taylor, D. V., & Amen, D. G. (2011). Decreased cerebral blood flow in the limbic and prefrontal cortex using SPECT imaging in a cohort of completed suicides. *Translational Psychiatry*, *1*(8), e28. https://doi.org/10.1038/tp.2011.28

Wingard, J. C., & Packard, M. G. (2008). The amygdala and emotional modulation of competition between cognitive and habit memory. *Behavioural Brain Research*, *193*(1), 126–131. https://doi.org/10.1016/j.bbr.2008.05.002

Wingenfeld, K., & Wolf, O. T. (2011). HPA Axis Alterations in Mental Disorders: Impact on Memory and its Relevance for Therapeutic Interventions: HPA Axis Alterations in Mental Disorders. *CNS Neuroscience & Therapeutics*, *17*(6), 714–722. https://doi.org/10.1111/j.1755-5949.2010.00207.x

Wixted, J. T., & Squire, L. R. (2011). The medial temporal lobe and the attributes of memory. *Trends in Cognitive Sciences*, *15*(5), 210–217. https://doi.org/10.1016/j.tics.2011.03.005

Wolf, O. T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica*, *127*(3), 513–531. https://doi.org/10.1016/j.actpsy.2007.08.002

Wolf, O. T. (2009). Stress and memory in humans: Twelve years of progress? *Brain Research*, *1293*, 142–154. https://doi.org/10.1016/j.brainres.2009.04.013

Wolf, O. T., Atsak, P., de Quervain, D. J., Roozendaal, B., & Wingenfeld, K. (2016). Stress and Memory: A Selective Review on Recent Developments in the Understanding of Stress Hormone Effects on Memory and Their Clinical Relevance. *Journal of Neuroendocrinology*, *28*(8). https://doi.org/10.1111/jne.12353

Wolkowitz, O. M., Burke, H., Epel, E. S., & Reus, V. I. (2009). Glucocorticoids: Mood, Memory, and Mechanisms. *Annals of the New York Academy of Sciences*, *1179*(1), 19–40. https://doi.org/10.1111/j.1749-6632.2009.04980.x

Wolkowitz, O. M., Rubinow, D., Doran, A. R., Breier, A., Berrettini, W. H., Kling, M. A., & Pickar, D. (1990). Prednisone effects on neurochemistry and behavior: preliminary findings. *Archives of General Psychiatry*, *47*(10), 963–968. Retrieved from http://archpsyc.jamanetwork.com/article.aspx?articleid=495131

Wood, L., Ducroq, D. H., Fraser, H. L., Gillingwater, S., Evans, C., Pickett, A. J., … Turkes, A. (2008). Measurement of urinary free cortisol by tandem mass spectrometry and comparison with results obtained by gas chromatography-mass spectrometry and two commercial immunoassays. *Annals of Clinical Biochemistry*, *45*(4), 380–388. https://doi.org/10.1258/acb.2007.007119

Woodard, J. L., Grafton, S. T., Votaw, J. R., Green, R. C., Dobraski, M. E., & Hoffman, J. M. (1998). Compensatory recruitment of neural resources during overt rehearsal of word lists in Alzheimer's disease. *Neuropsychology*, *12*(4), 491–504. https://doi.org/10.1037//0894-4105.12.4.491

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *NeuroImage*, *21*(4), 1732–1747. https://doi.org/10.1016/j.neuroimage.2003.12.023

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., … Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage*, *45*(1, Supplement 1), S173–S186. https://doi.org/10.1016/j.neuroimage.2008.10.055

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. *NeuroImage*, *14*(6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931

Wright, C. I., Wedig, M. M., Williams, D., Rauch, S. L., & Albert, M. S. (2006). Novel fearful faces activate the amygdala in healthy young and elderly adults. *Neurobiology of Aging*, *27*(2), 361–374. https://doi.org/10.1016/j.neurobiolaging.2005.01.014

Xing, Y., Hou, J., Meng, Q., Yang, M., Kurihara, H., & Tian, J. (2015). Novel antidepressant candidate RO-05 modulated glucocorticoid receptors activation and FKBP5 expression in chronic mild stress model in rats. *Neuroscience*, *290*, 255–265. https://doi.org/10.1016/j.neuroscience.2015.01.044

Yang, E., Zald, D. H., & Blake, R. (2007). Fearful expressions gain preferential access to awareness during continuous flash suppression. *Emotion (Washington, D.C.)*, *7*(4), 882–6. https://doi.org/10.1037/1528-3542.7.4.882

Yonelinas, A. P. (2001). Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study.

Young, A. H. (2006). Antiglucocoticoid Treatments for Depression. *Australian and New Zealand Journal of Psychiatry*, *40*(5), 402–405. https://doi.org/10.1080/j.1440-1614.2006.01813.x

Young, A. H. (2014). The Effects of HPA Axis Function on Cognition and Its Implications for the Pathophysiology of Bipolar Disorder: *Harvard Review of Psychiatry*, *22*(6), 331–333. https://doi.org/10.1097/HRP.0000000000000020

Young, A. H., Sahakian, B. J., Robbins, T. W., & Cowen, P. J. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology*, *145*(3), 260–266. Retrieved from http://link.springer.com/article/10.1007/s002130051057

Young, A. H., Sharpley, A. L., Campling, G. M., Hockney, R. A., & Cowen, P. J. (1994). Effects of hydrocortisone on brain 5-HT function and sleep. *Journal of Affective Disorders*, *32*(2), 139–146. https://doi.org/10.1016/0165-0327(94)90072-8

Young, K. D., Bellgowan, P. S. F., Bodurka, J., & Drevets, W. C. (2013). Behavioral and Neurophysiological Correlates of Autobiographical Memory Deficits in Patients With Depression and Individuals at High Risk for Depression. *JAMA Psychiatry*, *70*(7), 698. https://doi.org/10.1001/jamapsychiatry.2013.1189

Young, K. D., Drevets, W. C., Schulkin, J., & Erickson, K. (2011). Dose-dependent effects of hydrocortisone infusion on autobiographical memory recall. *Behavioral Neuroscience*, *125*(5), 735–741. https://doi.org/10.1037/a0024764

Young, K. D., Erickson, K., Nugent, A. C., Fromm, S. J., Mallinger, A. G., Furey, M. L., & Drevets, W. C. (2012). Functional anatomy of autobiographical memory recall deficits in depression. *Psychological Medicine*, *42*(2), 345–357. https://doi.org/10.1017/S0033291711001371

Young, K. D., Siegle, G. J., Bodurka, J., & Drevets, W. C. (2016). Amygdala Activity During Autobiographical Memory Recall in Depressed and Vulnerable Individuals: Association With Symptom Severity and Autobiographical Overgenerality. *American Journal of Psychiatry*, *173*(1), 78–89. https://doi.org/10.1176/appi.ajp.2015.15010119

Yuen, E. Y., Liu, W., Karatsoreos, I. N., Ren, Y., Feng, J., McEwen, B. S., & Yan, Z. (2011). Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. *Molecular Psychiatry*, *16*(2), 156–170. Retrieved from http://www.nature.com/mp/journal/v16/n2/abs/mp201050a.html

Zhang, T. Y., Labonté, B., Wen, X. L., Turecki, G., & Meaney, M. J. (2012). Epigenetic Mechanisms for the Early Environmental Regulation of Hippocampal Glucocorticoid Receptor Gene Expression in Rodents and Humans. *Neuropsychopharmacology*, *38*(1), 111–123. https://doi.org/10.1038/npp.2012.149

Zitnik, G. A., Curtis, A. L., Wood, S. K., Arner, J., & Valentino, R. J. (2015). Adolescent Social Stress Produces an Enduring Activation of the Rat Locus Coeruleus and Alters its Coherence with the Prefrontal Cortex. *Neuropsychopharmacology*. https://doi.org/10.1038/npp.2015.289

Zobel, A. W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F., & Ising, M. (2001). Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. *Journal of Psychiatric Research*, *35*(2), 83–94. https://doi.org/10.1016/S0022-3956(01)00013-9

Zobel, A. W., Schulze-Rauschenbach, S., von Widdern, O. C., Metten, M., Freymann, N., Grasmäder, K., … Maier, W. (2004). Improvement of working but not declarative memory is correlated with HPA normalization during antidepressant treatment. *Journal of Psychiatric Research*, *38*(4), 377–383. https://doi.org/10.1016/j.jpsychires.2003.12.002

Zobel, A. W., Yassouridis, A., Frieboes, R.-M., & Holsboer, F. (1999). Prediction of Medium-Term Outcome by Cortisol Response to the Combined Dexamethasone-CRH Test in Patients With Remitted Depression. *American Journal of Psychiatry*, *156*(6), 949–951. https://doi.org/10.1176/ajp.156.6.949

END OF THESIS