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The role of *FKBP5* genetics and epigenetics in mediating the effects of early life adversity on emotional processing brain regions in major depressive disorder

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DECLARATION

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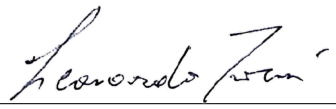

Leonardo Tozzi

SUMMARY

Major depressive disorder (MDD) is the most widespread psychiatric illness and is characterized by loss of pleasure, depressed mood, sleep disturbances and anxiety.

Recently, an inflammatory theory of MDD has emerged, which postulates that chronic dysregulation of the stress hormone axis and increased inflammation might be crucial in the pathogenesis of the disorder.

MDD shows genetic high-heritability. However, most association analyses investigating polymorphisms in MDD have so far met with conflicting results. The gene coding for FKBP5, a glucocordicoid receptor regulator protein, could play a role in vulnerability to MDD, especially in the presence of chronic environmental stressors such as childhood maltreatment.

Magnetic resonance imaging (MRI) is a safe and non-invasive technique that allows the investigation of the brain in vivo by using powerful magnetic fields. MDD patients show volume reduction, grey matter loss and altered function in regions that are crucial for emotional regulation.

The aim of our project was to investigate how genetics of *FKBP5* and childhood adversity might interact to explain structural and functional brain abnormalities in MDD patients. For this, we conducted studies on a database collected across two sites comprising a total of 104 MDD patients and 97 healthy controls.

First of all, we investigated which changes in activation and functional coupling were associated with MDD during an MRI task involving directing attention towards and away from the valence of emotional stimuli.

Secondly, we investigated whether patients carrying the high-risk allele of the rs1360780 *FKBP5* functional single nucleotide polymorphism showed differential activation during our task conditions compared to patients without genetic risk. We then sought to determine if these changes were mirrored by structural modifications and tested whether these could be explained by the interaction between genetic risk and exposure to childhood trauma.

Thirdly, we investigated epigenetic modifications of the *FKBP5* gene in depressed patients and controls. Previous studies have hypothe-

sised that chronic stress might functionally regulate *FKBP5* by methylation of its regulatory sites. We tested whether this modification was related to childhood adversity as well as to reduced grey matter and altered function in emotional processing areas.

Our results have confirmed that MDD patients show differences in activation in regions involved in emotional recognition. Functional connectivity between some of these areas and between ones belonging to the task-positive and default mode networks was also altered, in particular in trials involving regulation of negative emotions and recognition of positive ones.

Furthermore, we have shown that in patients carrying the high-risk allele of rs1360780, demethylation of the intron sites of the *FKBP5* gene promoter was correlated with the amount of early life maltreatment endured. There was no overall difference in methylation levels between patients and controls when rs1360780 and childhood adversity were not considered. Therefore we suggest that the presence of both genetic and environmental risk factors is able to produce lasting epigenetic changes in a gene that has a prominent role in glucocorticoid receptor regulation.

Childhood maltreatment also explained structural differences in temporal lobe white matter between MDD carrying different alleles of rs1360780. In addition to this, across our studies we have identified the inferior frontal lobe as a region whose structure and function are influenced by both *FKBP5* allelic status and methylation. Crucially, this area was less active during emotional recognition in MDD compared to controls and its activation was inversely correlated with depression severity.

Taken together, findings across our three studies provide evidence that the gene coding for the glucocorticoid regulator FKBP5 protein is a convergence point for the interplay between genetic and environmental risk factors of MDD. The size of the effects we detected ranged from small to moderate, suggesting that more and larger studies are needed to disentangle them from other potential confounding contributors to brain structure and function.

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ACRONYMS

5-HT	serotonin
5-HTR	serotonin receptor
5-HTT	serotnonin transporter
5-HTTLPR	serotnonin transporter linked polymorphic region
AAL	automatic anatomical labeling
ACC	anterior cingulate cortex
B_0	constant magnetic field
BDI	Beck depression inventory
BDNF	brain derived neurotrophic factor
BICC1	BicC family RNA Binding Protein 1
BMI	body mass index
BOLD	blood oxygen dependent signal
CAMI	centre for advanced medical imaging
CAT12	computational anatomy toolbox 12
CRP	C reactive protein
CSF	cerebrospinal fluid
CTQ	childhood trauma questionnaire
dACC	dorsal anterior cingulate cortex

DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
DMPFC	dorsomedial prefrontal cortex
DR	dopamine receptor
DSM-V	diagnostic and statistical manual of mental disorders 5^{th} edition
DTI	diffusion tensor imaging
EPI	echo planar imaging
ERT	emotion recognition trials
FA	fractional anisotropy
FDR	false detection rate
FKBP4	FK506 binding protein 4
FKBP5	FK506 binding protein 51
fMRI	functional magnetic resonance imaging
FWE	family wise error
FWHM	full-width at half maximum
GEE	generalized estimating equations
GLM	general linear model
GM	grey matter
gPPI	generalized psycho-physiological interaction
GR	glucocorticoid receptor
GRE	glucocorticoid response element
HAMD	Hamilton depression scale
HC	healthy controls
HPAA	hypothalamus-pituitary-adrenal axis
HRF	hemodynamic response function
hsp90	heat shock protein 90
IAPS	international affective pictures database
IFG	inferior frontal gyrus
IFGO	inferior frontal gyrus pars orbitalis
ITG	inferior temporal gyrus
MAOA	monoamine oxidase A enzyme
MAOI	monoaminoxidase inhibtor

MD	mean diffusivity
MDD	major depressive disorder
MFG	middle frontal gyrus
MNI	Montreal neurological institute
MRI	magnetic resonance imaging
NA	noradrenaline
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PCR	polymerase chain reaction
PET	positron emission tomography
pgACC	pregenual anterior cingulate cortex
PPI	psycho-physiological interaction
PSQI	Pittsburgh sleep quality index
PTSD	post traumatic stress disorder
RF	radiofrequency
ROI	region of interest
SCID-I	structured clinical interview for DSM disorders 1
SE-EPI	spin echo type echo planar imaging
SENSE	sensitivity encoding
SFG	superior frontal gyrus
sgACC	subgenual anterior cingulate cortex
SLC6A2	noradrenaline transporter
SNP	single nucleotide polymorphism
SNRI	serotonin-norepinephrine reuptake inhibitors
SPECT	single positron emisson tomography
SPM12	statistical parametric mapping 12
SPSS	statistical package for the social sciences
SRT	shape recognition trials
SSRI	selective serotonin reuptake inhibitor
T1	time of longitudinal relaxation
T2	time of transverse relaxation
T2*	time of transverse relaxation in tissues
TCA	tricyclic antidepressant

TCIN	Trinity College institute of neuroscience
TE	time of echo
TIV	total intracranial volume
TPH	tryptophan hydroxylase
TR	time of repetition
TPR	tetratricopeptide repeat protein
VBM	voxel-based morphometry
VLPFC	venterolateral prefrontal cortex
VMPFC	venteromedial prefrontal cortex
VNTR	variable tandem number repeat
WM	white matter

Part I

INTRODUCTION

1

MAJOR DEPRESSIVE DISORDER

1.1 EPIDEMIOLOGY

Major Depressive Disorder (MDD) is a widespread psychiatric illness in the general population, with a global prevalence that is highly variable depending on the sample (from 4% up to 15%) and an annual incidence of around 3% (Kessler et al., 2003; Ferrari et al., 2013). It currently constitutes a significant public health issue and the World Health Organization has ranked it as the third leading cause of disease burden worldwide (Colin Mathers, Doris Ma Fat, 2008).

Epidemiological investigations report an age of onset around 25 years, with risk increasing linearly thereafter (Kessler et al., 2003; Christie et al., 1988; Blazer et al., 1994). Concerning the role of sex, the prevalence of major depressive episodes during lifetime is higher in women than men (Alonso et al., 2004; Blazer et al., 1994; Kessler et al., 2003; Patten et al., 2006), but this association becomes weaker with age and almost disappears when considering patients over 75 (Patten et al., 2016).

MDD is frequently co-morbid with other psychiatric conditions, such as anxiety disorders (Gao et al., 2013), substance abuse (Blanco et al., 2012) and other depressive conditions such as dysthymia (King-Kallimanis, Gum, and Kohn, 2009). Chronic medical illnesses are also often present in depressed patients (Wells, Golding, and Burnam, 1988; Moldin et al., 1993; Patten, 1999; Gagnon and Patten, 2002), especially those involving pain (e.g., multiple pains, fibromyalgia, headaches, back pain), inflammation (e.g., arthritis, asthma, heart disease) and, although to a lesser extent, other conditions such as cancer, diabetes and hypertension (Patten et al., 2016; Patten et al., 2005; Scott et al., 2007).

Furthermore, environmental factors can increase risk of MDD and a wide body of research has particularly highlighted the importance of low socio-economic status (Lorant et al., 2007; Lorant et al., 2003; Dohrenwend et al., 1992; Weich and Lewis, 1998) and acute adverse life events (Brown and Harris, 1979; Brown, Harris, and Hepworth, 1994; Swindle, Cronkite, and Moos, 1989). Psychological abuse and

neglect during childhood, in particular, have been shown to be particularly associated with depression later in life (Infurna et al., 2016).

Finally, genetic predisposition also plays a role in the disorder, regardless of environmental risks (Kendler et al., 1992), with twin studies suggesting a heritability of 40% to 50%, and family investigations indicating a twofold to threefold increase among first-degree relatives of MDD patients (Lohoff, 2010).

1.2 DIAGNOSIS

According the most recent edition of the diagnostic and statistical manual of mental disorders 5^{th} edition (DSM-V) published by the American Psychiatric Association (APA, 2013), a diagnosis of MDD must satisfy a list of criteria (see Table 1). Especially critical is the presence of anhedonia or depressed mood for an extended period of time as well as the lack of any comorbidity that might explain the symptoms. Other conditions include changes in appetite, sleep disturbances and somatic manifestations of anxiety.

1.3 ETIOLOGY

Even though many treatment options and hypotheses have emerged in the past years concerning the pathogenetic mechanisms underlying MDD , a definitive answer to the matter remains elusive (Kupfer, Frank, and Phillips, 2012).

1.3.1 *The monoamine hypothesis*

Historically, the first neurobiological theory regarding the disorder was formulated in the late 50s, when monoaminoxidase inhibtor (MAOI) and tricyclic antidepressant (TCA) drugs were fortuitously discovered. These drugs respectively inhibit the breakdown of monoaminergic neurotransmitters and their uptake in the synaptic cleft, leading to an increase of their overall availability, in particular concerning serotonin (5-HT) and noradrenaline (NA). Both MAOIs and TCAs were found to improve symptoms in depressed patients and provided clinicians with the first specific drugs for the treatment of MDD , which led to the hypothesis that a deficit of monoaminergic transmission might be the prime cause of the disease (Chopra, Kumar, and Kuhad, 2011). Subsequently, in the 80s a new generation of antidepressants was

A. At least five of the following during a 2-week period and at least one of the symptoms is (1) or (2):
1. Depressed mood almost daily and for most of the day, indicated by patient's subjective report or that of others. This state might be characterized by sadness, feeling of emptiness, or hopelessness.
2. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
3. Markedly diminished interest or pleasure activities along with the mood change (anhedonia).
4. Fatigue or loss of energy.
5. Significant weight loss when not dieting or, conversely, unaccounted weight gain.
6. Persistent inability to sleep or oversleeping.
7. Psychomotor agitation or retardation.
8. Diminished ability to think or concentrate, indecisiveness.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide.
B. Clinically significant distress or impairment in social, occupational, or other important areas of behaviour.
C. No evidence of substance abuse or of an underlying medical condition.
D. No evidence of schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other psychotic disorders.
E. Absence of a manic episode or a hypomanic episode.

Table 1 – Diagnosis of major depressive disorder. Criteria A-E must be satisfied for the diagnosis of Major Depressive Disorder as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (APA, 2013).

developed to specifically inhibit the reuptake of serotonin (selective serotonin reuptake inhibitor (SSRI)). These drugs are still used as a first line treatment for the disease today, since they show little or no activity on noradrenergic neurotransmitters, guaranteeing a better safety profile (Nestler, 1998).

After these discoveries and with the growing use of SSRIs in everyday clinical practice, the pathophysiology of depression has been dominated by the monoamine hypothesis for several years (Van Praag, 2001). During this time, many studies have tried to detect a monoaminergic deficit in MDD patients. Some were indeed successful in measuring reduced monoamine availability in *post-mortem* brain tissue and body fluids (Young et al., 1994; Leonard, 2000), but overall results appear so far inconsistent (Chopra, Kumar, and Kuhad, 2011). Also the tyrosine and tryptophan hydroxylases, two enzymes involved respectively in 5-HT and NA synthesis, were sometimes found to be

decreased in *post-mortem* brain samples, but not consistently across studies (Delgado and Moreno, 2000).

Thus, reduced monoaminergic function may not be present in the brain of all depressed patients. Also, variations of neurotransmitters in blood or cerebrospinal fluid (CSF) may not be relevant for local changes in specific brain circuits whose alterations might explain the symptoms (Delgado and Moreno, 2000).

Since the hypothesis of a global deficit of the 5-HT andNA systems in MDD started to seem unlikely, subsequent research focused on the role of transport proteins which decrease the availability of neurotransmitters in the synaptic cleft and reduce their effect on pre-synaptic and post-synaptic receptors. These same molecules are targeted by SSRIs and are expressed on human platelets as well as in the central nervous system, providing a model for their study *SNP* (Owens et al., 2008). Although studies have reported a decreased transporter function in MDD using the platelet model, results with *post-mortem* brain samples have not been as conclusive (Owens and Nemeroff, 1994). *In vivo* investigations with single positron emisson tomography (SPECT), however, were able to confirm a reduced number of 5-HT transporters in the midbrain of MDD patients (Staley, Malison, and Innis, 1998). Successive studies imaging selective serotnonin transporter (5-HTT) ligands using positron emission tomography (PET) have also found reduced levels of the transporter in serotoninergic areas in highly negativistic patients (Meyer et al., 2004) as well as lower 5-HTT availability binding potential in the amygdala (Parsey et al., 2006) and increased transporter availability in the left frontal cortex and right cingulate cortex among drug-free patients (Reivich et al., 2004). Availability of 5-HTT was also found to be higher in the thalamus and striatum of patients (Cannon et al., 2007). Genetics studies have also shown that alleles leading to reduced expression of these molecules are found more frequently in depressed patients and are correlated to specific changes in brain structure and function (Bellivier et al., 1998; Caspi et al., 2003; Frodl et al., 2010a), which will be reviewed in detail in Chapter 2 and Chapter 5.

All this evidence seems to point toward a deficit of monoaminergic transmission in MDD, probably at the transporter level, but in time a few observations pointed out that its facilitation could not be the only mechanism leading to clinical improvement during antidepressant treatment. First of all, the therapeutic actions of SSRIs, TCAs and MAOIs all take several weeks to become apparent, despite the attain-

ment of effective blood and brain levels even after short term administration (Hyman and Nestler, 1996). Thus, it is possible that the action of these drugs could be responsible for eliciting and maintaining specific secondary brain adaptations that improve depressive mood. Secondly, several years of research on monoamine metabolite levels in MDD have to this date failed to establish a cohesive model of the pathology. Finally, the efficacy of monoamine-targeted therapeutic agents in several other psychiatric disorders, such as panic disorder, obsessive-compulsive disorder, bulimia, enuresis and chronic pain, suggests that an impairment of the monoaminergic system might be a final common pathway which is not exclusive of depression (Nestler, 1998).

Since the depletion of monoaminergic neurotransmitters has not proven sufficient to this day in elucidating the causes that could lead to MDD , research has more recently focused on the finding that systemic inflammatory regulation and the endocrine stress axis also seem to be impaired in patients suffering from MDD (Miller, Maletic, and Raison, 2009). This observation has led to an inflammatory hypothesis of the pathogenesis of MDD, according to which a dysregulation of endocrine, inflammatory and neurotrophic factors leads to alterations in brain structure and function.

1.3.2 *The inflammatory hypothesis*

Stress is a physiological response of the organism to potentially threatening situations and it involves the activation of the hypothalamus pituitary adrenal axis (HPAA), leading to the secretion of cortisol. This hormone then acts through mineralocorticoid and glucocorticoid receptor (GR) on several organs throughout the body to catabolize energy resources and inhibit inflammatory responses (de Kloet, Joëls, and Holsboer, 2005).

Clinical evidence for a role of glucocorticoid hormones in depression has long been suspected (Carpenter and Bunney, 1971; Czéh et al., 2001; Gibbons and McHugh, 1962). Indeed, depressive symptoms are a common side effect of long term corticosteroid treatment (Patten, Williams, and Love, 1995) and, conversely, normalization of hormone levels in Cushing syndrome improves patients' mood (Sonino et al., 1993). Furthermore, signs of a hyper-activation of the HPAA are found in many depressed patients (Nestler, 1998), as well as impaired response to dexamethasone suppression, adrenal gland hyper-

plasia (Rubin et al., 1995), blunted adenocorticotropic hormone and increased cortisol release after CRF stimulation (Holsboer et al., 1986). A higher secretion of this hormone following administration of dexamethasone has also been detected in non depressed patients with high family risk for depression, suggesting that genetic regulation of the HPAA might be involved in determining vulnerability to MDD (Holsboer et al., 1995).

Compatibly with the hypothesis of a role of stress hormones in the pathogenesis of MDD, antidepressant treatment has been shown to decrease cortisol levels (Schüle et al., 2009) and improve dexamethasone suppression test performance in MDD patients (Nikisch et al., 2005). Also, within the brain, GRs are expressed in regions such as the hippocampus, amygdala and prefrontal cortex (Reul and de Kloet, 1985), which can regulate the HPAA itself through feedback mechanisms (Herman et al., 2005). These areas are involved in cognition as well as mood regulation and are functionally and structurally altered in MDD (see Chapter 4).

Aside from stress hormones, cytokines also seem to play a role in depression (Jackson and Luo, 1998; Hughes, Connor, and Harkin, 2016). It has been observed that patients treated with interferons and interleukin 2 for other conditions show depression-like symptoms (Dunn, Swiergiel, and Beaurepaire, 2005; Miller et al., 1996) and that disorders featuring inflammation are more strongly associated with MDD compared to other chronic conditions (Patten et al., 2016). Furthermore, the increased secretion of pro-inflammatory cytokines seems to be associated with the HPAA dysregulation observed in depressed patients cohorts and is reversed by treatment (Kim et al., 2007).

It is not yet clear how changes in HPAA function and cytokine levels might ultimately lead to MDD, although current hypotheses involve the dysregulation of neurotrophic factors that might have an impact on the structure and function of specific brain areas. The hippocampus, for example, has been extensively studied in this regard, since it shows a reduced volume in patients with MDD (see Chapter 4). In animal models, atrophy of this structure (Magariños, Deslandes, and McEwen, 1999; McEwen, 1999; McKittrick et al., 2000) and a decrease in neurogenesis in it have been shown in response to a high level of glucocorticoids (Gibbons and McHugh, 1962; Gould et al., 1997). Conversely, antidepressant treatment and electroconvulsive therapy have

been shown to increase neurogenesis in the hippocampus (Malberg et al., 2000; Malberg, 2004).

How cell loss in the hippocampus could be linked to HPAA and cytokine dysregulation is still a matter of debate. It has been suggested, however, that it might be a consequence of the fact that glucocorticoids and inflammation suppress neurogenesis factors such as the brain derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin 3 and vascular endothelial growth factor (Duman and Monteggia, 2006; Dwivedi et al., 2003; Ueyama et al., 1997; Heine et al., 2005). BDNF, in particular, is reduced in the brain (Chen et al., 2001; Dwivedi et al., 2003; Karege et al., 2005) and in the blood of depressed patients (Karege et al., 2002). Interestingly, chronic administration of antidepressants can reverse this effect and restore BDNF to its former levels (Aydemir, Deveci, and Taneli, 2005; Gervasoni et al., 2005; Nibuya, Morinobu, and Duman, 1995; Duman, 1998; Gonul et al., 2005).

1.3.3 *Childhood adversity and inflammation*

As previously mentioned, early psychological abuse and neglect are especially associated with adult depression (Infurna et al., 2016). An expanding body of evidence (see Kuhlman et al., 2017 for a recent review) suggests this link might be mediated by long-term alterations of the HPAA and inflammatory regulation. These might be induced by its exaggerated activation during childhood and adolescence, which are especially sensitive times in which the axis is going through major functional changes (Kuhlman et al., 2017).

Different forms of childhood adversity have been investigated in this regard. Concerning physical abuse, for example, infants (Bugental, Martorell, and Barraza, 2003) and children (Kuhlman, Olson, and Lopez-Duran, 2014) exposed to it show increased cortisol responses to psychological as well as psychosocial stress (Kuhlman et al., 2015). Youth exposed to sexual abuse, on the other hand, exhibit elevated circulating baseline plasma cortisol compared to controls (Simsek et al., 2015). Negative parenting behaviours involving neglect of the offspring are also associated with flat diurnal cortisol slopes throughout the day in infants (Koss et al., 2014), elevated cortisol during middle childhood (Ashman et al., 2002; Essex et al., 2002) and impaired down-regulation of cortisol following peak response to acute psychological stress (Kuhlman, Olson, and Lopez-Duran, 2014). These im-

pairements appear to persist into adulthood (Nicolson, 2004; Kumari et al., 2013; Tyrka et al., 2008).

Other studies have investigated the link between these alterations of the HPAA and inflammatory responses. For example, children exposed to physical maltreatment who also have symptoms of depression have elevated C reactive protein (CRP) (Danese et al., 2009). Exposure to bullying during childhood and adolescence is associated with elevated CRP during early (Copeland et al., 2014) and middle adulthood (Takizawa et al., 2015). Overall, experiencing multiple types of maltreatment before adulthood was found to be associated with elevated CRP, fibrinogen, and proinflammatory cytokines (Coelho et al., 2014).

1.4 CONCLUSIONS

To sum up, MDD is the most widespread psychiatric disorder and is characterized by loss of pleasure, depressed mood, sleep disturbances and anxiety (Ferrari et al., 2013).

It affects females more than men, its incidence increases with age and it is frequently comorbid with chronic medical conditions, especially those involving inflammation (Patten et al., 2016). Environmental stressors, such as lower socio-economic status and adverse life events also increase the risk of developing it (Lorant et al., 2007; Brown and Harris, 1979).

Biologically, MDD is characterized by deficits in the monoaminergic system, which could explain how the most successful drugs to treat it so far have been those inhibiting the reuptake of serotonin in the synaptic cleft. The monoaminergic hypothesis, however, has been unable to explain the slow onset of medication effects, the wide spectrum of disorders for which these are beneficial and contradictory findings in clinical and preclinical studies on monoamine concentration in patients' brains (Nestler, 1998).

Recently, an inflammatory theory of MDD has emerged, which postulates that chronic dysregulation of the stress hormone axis and increased inflammation might be crucial in the disorder. In particular, these might reduce the concentration or function of neurotrophic factors in brain areas that are crucial for emotional regulation, such as the hippocampus and prefrontal cortex, leading to depressive symptoms over time (Miller, Maletic, and Raison, 2009). This theory might also clarify the increased incidence of MDD among people who are

maltreated during childhood, since early life adversity has been shown to impair HPAA function and inflammatory regulation.

2

GENETICS OF MAJOR DEPRESSION

As an essential part of research on MDD, many studies have focused on finding associations between the disease and genetic factors. Ultimately, the goal is to gain a better insight into interactions that might help define subsets of patients at risk or more likely to respond to certain therapies.

Genome-wide studies seeking single nucleotide polymorphism (SNP)s associated with MDD had often negative and at best mixed results, possibly because of the key importance of environmental factors in the disorder (see Dunn et al., 2015 for a review). Therefore, the genetic variants associated with MDD for which more evidence is available are still those obtained from smaller hypothesis-driven studies, which have targeted genes based on the current pathogenetic theories.

The first studies of this kind have primarily focused on genes involved in the synthesis of monoaminergic neurotransmitters, such as the monoamine oxidase A enzyme (MAOA) (Schulze et al., 2000)) and tryptophan hydroxylase (TPH) 1 genes (Gizatullin et al., 2006). Other studies have also focused on molecules involved in their synaptic function, such as their transporters and receptors (Bellivier et al., 1998; Caspi et al., 2003; Frodl et al., 2010a; López-León et al., 2008).

Later, given the relationship between endocrine stress and depression (Charney and Manji, 2004), genetic polymorphisms associated with anomalies of HPAA regulation have also been investigated, such as those of the *FK506 binding protein 51 (FKBP5)*.

Finally, studies investigated mediators of neuronal plasticity such as BDNF (Arlt et al., 2013; Lavebratt et al., 2010), compatibly with their reduced secretion in MDD (Duman and Monteggia, 2006).

A brief overview of the findings from these studies will now be presented (for a detailed review, see Cohen-Woods, Craig, and McGuffin, 2013).

2.1.1 *Monoamine oxidase*

The MAOA enzyme plays a role in the degradation of biological amines, such as serotonin, noradrenaline and dopamine (Syagailo et al., 2001; Youdim, Edmondson, and Tipton, 2006). Its gene is located on chromosome Xp11.23-p11.4 (Ozelius et al., 1988; Levy et al., 1989).

Two functional polymorphisms of *MAOA* have been studied in relation to depression. The first was a SNP, which was not found to be associated with the disorder (Sasaki et al., 1998; Kersting et al., 2007; Zhang et al., 2010) but the second, a variable tandem number repeat (VNTR), provided encouraging results (Rivera et al., 2009; Brummett et al., 2007) especially in females (Schulze et al., 2000). Other studies, even if not confirming this finding, still found a suggestive role of *MAOA* genetic variation in depression symptomatology (Christiansen et al., 2007), although others denied it completely (Kunugi et al., 1999).

2.1.2 *Tryptophan hydroxilase*

TPH1 limits the biosynthesis of serotonin (Priestley and Cuello, 1982) and is coded by a gene mapped to human chromosome 11p15.3-p14 (Craig et al., 1991).

Associations between variants in the A218C (rs1800532) SNP of this gene and MDD have been reported (Viikki et al., 2010; Wang et al., 2011) and might play a role in susceptibility and acute response to treatment (Vadnal, Parthasarathy, and Parthasarathy, 2012). These findings, however, have not been confirmed at a meta-analytic level (López-León et al., 2008).

A second SNP in intron 7 of *TPH1* has been associated with MDD (Gizatullin et al., 2006), although this finding was not present in a similar study published in the same year (Kõks et al., 2006).

TPH2 is a second isoform of the enzyme, located in 12q21 within a previously reported MDD linkage region (Abkevich et al., 2003). A very rare mutation associated with functional loss of this enzyme was found to be associated with MDD (Zhang et al., 2005). After a failed attempt of replication of these results, however, Glatt et al., 2005 concluded that this variant is not likely to play a role in the

general MDD population, but might be involved in rare familial forms of the disorder.

2.1.3 *Serotonin transporter*

The gene coding for the 5-HTT is located at 17q11.1-q12 and has a few well-characterized polymorphisms. The first one is situated at the 5' flanking regulatory region of the gene, and consists of a 44 base pair insertion-deletion polymorphism, the serotnonin transporter linked polymorphic region (5-HTTLPR) (Heils et al., 1996).

The long and short variants of SNP are associated with different levels of 5-HTT expression and serotonin reuptake (Lesch et al., 1996). Meta-analyses assessing the effects of this region across several studies have returned inconsistent results, with two works confirming the association between its short variant and MDD (Lotrich and Pollock, 2004; López-León et al., 2008) but others not being able to replicate it (Anguelova, Benkelfat, and Turecki, 2003; Willis-Owen et al., 2005).

Other studies have investigated another SNP, rs25531 (A/G), which influences transcriptional activity as part of a haplotype with variants of the 5-HTTLPR (Nakamura et al., 2000). In particular, a meta-analysis has reported an association between the less active haplotype with depression (Kiyohara and Yoshimasu, 2010). The more active variant, on the other hand, might be predictive of treatment response (Bonvicini et al., 2010; Kraft et al., 2005; Ruhé et al., 2009; Smeraldi et al., 2006). Furthermore, other studies describe even more neighbouring polymorphisms that might have an impact on the gene's transcription (Martin et al., 2007).

A 16/17 bp VNTR in the second intron of *5-HTT* has also been investigated (Cowen and Charig, 1987; Kaiser et al., 2001). Some association studies have shown a link with a 9 repeat variant (Battersby et al., 1996; Ogilvie et al., 1996; Bozina et al., 2006), but others have contradicted these findings (Kunugi et al., 1999; Furlong et al., 1998). In any case, meta-analyses have still failed to find a significant association between polymorphisms of this region and depression (Furlong et al., 1998; Anguelova, Benkelfat, and Turecki, 2003; López-León et al., 2008).

2.1.4 *Serotonin receptor*

Several classes of the serotonin receptor (5-HTR) have been investigated throughout the years.

Concerning the gene coding for 5-HTR 1A, this sequence is located at 5aqq.2-q13 (Melmer et al., 1991) and there is little evidence for its association with MDD (López-León et al., 2008).

On the other hand, *5-HTR 1B* maps to human chromosome 6q13, a region for which linkage to depression and anxiety has been shown in males (Holmans et al., 2004; Nash et al., 2004). A functional polymorphism in this gene has been identified (Maura et al., 1993), but it has not been found to be associated with MDD in general, although it might play a role in the most severe forms of the disorder (Huang et al., 2003).

Studies on the 5-HTR 2A gene (*HTR2A*) have also been inconclusive, showing no influence of variations on function (Anguelova, Benkelfat, and Turecki, 2003; López-León et al., 2008).

The 5-HTR 2C gene on chromosome Xq24 did show a functional polymorphism (Lappalainen et al., 1995; Quested et al., 1999), but no convincing evidence for its variants and MDD exists (Lerer et al., 2001; Kõks et al., 2006).

In the *5-HTR 3B* gene, one study could find an association between a haplotype and MDD, although the finding was limited to japanese females (Yamada et al., 2006).

Finally, no evidence for association was found for *5-HTR 5A* and *HTR6* (Cohen-Woods, Craig, and McGuffin, 2013).

2.1.5 *Noradrenaline*

Serotonin-norepinephrine reuptake inhibitors (SNRI) are antidepressants that act on the noradrenaline transporter (SLC6A2), which has been shown to be hypoexpressed in the locus coeruleus of depressed patients (Klimek et al., 1997).

The gene coding for this protein is located on the chromosome 16q12.2 (Porzgen, Bonisch, and Bruss, 1995). A polymorphism in its promoter was found to be associated with depression, although studies did not agree on which variant showed the effect (Inoue et al., 2004; Ryu et al., 2004). Also, other studies (Owen et al., 1999; Inoue et al., 2007) and a meta-analysis (López-León et al., 2008) did not find any results at all for *SLC6A2*. A potential explanation for the contra-

dictory findings came from a study which re-sequenced the exons in an ethnic minority group and found a significant link, highlighting the importance of accounting for genetic variabilities within populations (Dong, Wong, and Licinio, 2009).

Concerning adrenergic receptors, no association was found between polymorphisms in their genes and MDD (Ohara et al., 1998; Zill et al., 2003; Zubenko et al., 2003; Burcescu et al., 2006).

2.1.6 *Dopamine*

The dopamine transporter has a VNTR in its three prime untranslated region and the 9/10 genotype was found to be suggestively associated with MDD at the meta-analytic level (López-León et al., 2008).

Concerning dopamine receptors dopamine receptor (DR)D1 and DRD2, polymorphisms in their genes were not found to be associated to MDD (Garriock et al., 2006; Kõks et al., 2006; Manki et al., 1996; Furlong et al., 1998).

One study, however, reported a link with a polymorphism of *DRD3* (Dikeos et al., 1999), but this was not replicated by successive investigations (Manki et al., 1996; Garriock et al., 2006).

Finally, in the *DRD4* gene, a VNTR has been found to be associated with depression (Manki et al., 1996) but this finding was shown to be inconsistent as well (Oruc et al., 1997; Frisch et al., 1999).

2.2 BRAIN-DERIVED NEUROTROPHIC FACTOR

The *BDNF* gene is mapped at 11p13/11p14 (Hanson, Seawright, and van Heyningen, 1992). Reports have been conflicting but a large case-control study reported a haplotype association in two independent samples of MDD and schizophrenia patients with depressive symptoms (Schumacher et al., 2005). Subsequent meta-analyses, however, have produced conflicting results highlighting potential effects of gender and ethnicity (Gratacòs et al., 2007; Verhagen et al., 2010).

2.3 FK506 BINDING PROTEIN 51

Given the hypothesis of an immune response dysfunction in MDD, recent data have shown an association between the disease and allelic variants of genes involved in GR regulation. After binding its ligand, GR acts as a transcription factor, by translocating from the cytosol

to the nucleus and inducing gene transcription. This phenomenon is mediated by a large molecular complex, involving the chaperones of heatshock protein 70 (hsp70) and 90 (hsp90) (Pratt and Toft, 1997; Pratt et al., 2006). This structure is essential for proper folding and trafficking to the nucleus of the receptor and for its subsequent binding to the DNA (Grad and Picard, 2007). Thus, alterations in any of the molecules that are involved in this process may have an impact on GR sensitivity and, potentially, be candidates for the pathophysiology of mood disorders.

In particular, the FKBP5 is a 51 kDa protein that acts as an important functional regulator of the GR complex (Grad and Picard, 2007; Pratt and Toft, 1997). It belongs to the peptidyl prolyl isomerase superfamily and to the tetratricopeptide repeat protein (TPR)-containing immunophilins. FKBP5 is involved in the assembly of the heat shock protein 90 (hsp90)-steroid receptor complex (Schiene-Fischer and Yu, 2001), acting as a co-chaperone. During the maturation of the complex, FKBP5 binds to hsp90 via a TPR-domain that then serves as a ligand site for other co-chaperones. In this conformation, the receptor complex has lower affinity for cortisol (Wochnik et al., 2005) and its nuclear translocation is less efficient (Binder, 2009). After the GR has bound its ligand, FKBP5 is exchanged against another TPR-containing immunophilin the FK506 binding protein 4 (FKBP4), which then recruits dynein into the complex, allowing its nuclear translocation and transcriptional activity (Davies, Ning, and Sánchez, 2002; Wochnik et al., 2005).

In addition to its role in determining cortisol affinity of the receptor, FKBP5 may also promote the nuclear translocation of its non-active beta-isoform, thereby decreasing overall GR signalling (Zhang, Clark, and Yorio, 2008).

The gene encoding FKBP5 is located on the short arm of human chromosome 6 (chromosome 6p21.31) (Nair et al., 1997) and variations in its sequence seem to be relevant for GR function. The single nuclear polymorphism (SNP) rs1360780 in this gene, for example, has been associated with increased FKBP5 expression and changes in peripheral FKBP5 mRNA (Binder et al., 2004). These alleles have also been correlated with a relative inhibition of the binding of cortisol to GRs in monkeys (Denny et al., 2000; Scammell et al., 2001). This phenomenon might be responsible for the finding that healthy individuals who are homozygous for the high-induction alleles show

slower recovery of stress-related increases in cortisol levels and more anxiety symptoms during recovery (Ising et al., 2008).

Allelic variants in *FKBP5* have also been found to be associated with MDD (Gillespie et al., 2009) and increased risk of developing the disease (Suzuki et al., 2014), although these results have not always been repeatable (Lavebratt et al., 2010). SNPs in rs1360780 seem to be especially involved, with the presence of allele T and genotype TT being reportedly associated with depression (Lavebratt et al., 2010; Gillespie et al., 2009). Associations between this SNP and antidepressant treatment responses were also reported, but they were not confirmed at the metanalytic level (Niitsu et al., 2013). Further studies revealed an association between the same genotype and MDD in specific patient cohorts such as gastric cancer patients (Kang et al., 2012) and kidney transplant recipients (Gen S., 2011). It is possible that the effect of this gene could then become significant towards the development of the disease following its interaction with a significant amount of chronic stress, such as the one undergone by gastric cancer patients (Kang et al., 2012) or victims of childhood abuse (Gillespie et al., 2009), although other studies have reported no findings in this regard (Shimasaki et al., 2014; Van der Auwera et al., 2018). Indeed, other studies have investigated how interaction between genetic factors and stressful environmental variables such as early life adversity can impact on brain function and anatomy in depressed patients (Bermingham et al., 2012; Frodl et al., 2010a). Specifically, a significant association has been reported between depression, *FKBP5* risk allele carrier status (minor allele T) and an impaired regulation of the endocrine HPA axis (Menke et al., 2013).

2.4 CONCLUSIONS

MDD shows high-heritability (Lohoff, 2010). However, most association analyses that have been performed investigating polymorphisms in MDD have so far met with conflicting results, both concerning genes coding for proteins involved in monoaminergic transmission and growth factors. This suggests that very large sample sizes might be required to detect common variations of small effects or the existence of complex interactions with elements such as ethnicity and gender (Sullivan, 2012; Cohen-Woods, Craig, and McGuffin, 2013).

The gene coding for FKBP5, a GR regulator protein, could play a role in HPAA dysregulation and vulnerability to MDD, especially in the

presence of environmental stressors (Flint and Kendler, 2014; Bosker et al., 2011; Clarke et al., 2010; Cohen-Woods, Craig, and McGuffin, 2013; Gyekis et al., 2013).

3

MAGNETIC RESONANCE IMAGING

3.1 GENERAL PRINCIPLES

For a basic introduction to the method, see Currie et al., 2013. In summary, magnetic resonance imaging (MRI) is a technique based on the physical principle of nuclear resonance.

Since the methodology itself is not limited to studying the brain, scanner characteristics can vary greatly according to the procedure's purpose. Overall, an MRI scanner comprises a set of main magnet coils, three gradient coils, shim coils and an integral radio frequency (RF) coil (Ridgway, 2010).

The main magnet coils, made of a superconducting metal-alloy, are cooled close to absolute zero, (around 4°K or -269°C) using liquid helium (Jacobs, Ibrahim, and Ouwerkerk, 2007). These coils generate a strong constant magnetic field (B_0), whose intensity can vary and is correlated to the final spatial resolution of the acquired images. Low intensity scanners, for example, are routinely employed in the study of joints and organs such as the kidneys and heart. In brain imaging, however, higher intensity magnetic fields are usually needed. For scanners employed in the clinic, such as those used to detect brain abnormalities (e.g. tumours or strokes), a field strength of 1.5 T is usually sufficient. For research purposes, on the other hand, a 3 T field strength leads to the acquisition of higher resolution images, which allow accurate discrimination of brain areas to investigate their structure and function. Some devices currently used in neuroimaging research can even reach up to 7 T field strength and scanners are being developed that can reach 8 or 9 T to achieve even better spatial resolution.

The gradient coils lie concentric to each other within the main magnet, along the three orthogonal directions (x, y and z). Each one is capable of generating a magnetic field in the same direction as the main one, but with a strength that changes with position along the x, y or z directions, depending on which gradient coil is used (Currie et al., 2013).

Shimming coils ensure the static magnetic field homogeneity after the participant has entered the scanner.

Finally, radio-frequency (RF) coils generate energy of frequency within the megahertz range and are mounted concentrically inside the gradient coils. They have two main purposes: to transmit RF energy to the tissue of interest and to receive induced RF signal back from it. For neuroimaging, a separate RF receiver coil that is tailored to maximise the signal from the brain is usually applied around the patient's head to detect the emitted MR signals (Jacobs, Ibrahim, and Ouwerkerk, 2007). The output picked up by the receiver coil is digitised and then sent to a reconstruction computer processor to yield the final image (Hahn, 1950).

For a schematic representation of how the MR signal is generated, see Figure 1.

In summary, while being immersed in the strong static magnetic field generated by the main coils, protons in the patient's body tend to align their spin parallel or anti-parallel to it. During this process, spins acquire a precession movement around the magnetic field's direction that has a frequency determined by the nuclear species and the intensity of the magnetic field (Larmor frequency). Then, the participant's body is exposed to a RF pulse having the same frequency as the Larmor frequency of the protons, disturbing them so that their spin falls out of alignment with B_0. This phenomenon is called magnetic resonance (Currie et al., 2013).

After the second field has been administered, it is removed when the proton spins have reached the desired alignment, so that they will go back to their original orientation (relaxation), inducing an electrical current in the receiver RF coil, which is detected (Currie et al., 2013).

Detection is usually conducted one sagittal slice at the time, so that the entire brain volume is reconstructed in three dimensions after all the images have been merged together. The thickness of each slice can be set, with thinner slices leading to a higher image resolution but a longer acquisition time for the entire volume. Dimensions of the final volumetric unit (voxel) of the image will depend on this setting and will determine its spatial resolution.

According to the radio-frequencies used and to the time at which the subsequent signal is detected, tailored sequences can be used for different purposes. Also, it is possible to measure the signal obtained from the resonance of protons from a great variety of atomic nuclei,

such as sodium, phosphorus, carbon and hydrogen, setting the resonance frequency at the appropriate value. However, as a source of signal, hydrogen is currently used almost exclusively.

3.2 STRUCTURAL MAGNETIC RESONANCE

The first sequences that are almost invariably used in a neuroimaging experiment are the ones that allow the acquisition of a highly detailed anatomical image of the participant's brain. For this purpose, two time constants are usually considered of interest after removal of the second magnetic field: the first (time of longitudinal relaxation (T1)) measures how fast the original magnetization along the main field's direction is reinstated, the second (T2) measures how long it takes for the spins to lose their transversal magnetization component.

Free water has a small molecular size and tumbles much too quickly to be detected at T1, making its T1 relaxation time long (Currie et al., 2013). Similarly, hydrogen protons bound to large macromolecules (e.g. membrane lipids) recover their original magnetization state very slowly. On the other hand, when water is partially bound (e.g. to proteins), its tumbling rate slows to a rate more in line with the Larmor frequency, making its T1 value much lower than the one of free water (Elster, 1994; Smith and Ranallo, 1989). Fat typically has a short T1 value since the carbon bonds at the ends of the fatty acids have frequencies near the Larmor frequency (Schild, 1990). Similarly to T1, tissues have different T2 values: brain, for example, has a shorter T2 than cerebrospinal fluid (Currie et al., 2013).

According to the signal detected in each voxel at T1 and time of transverse relaxation (T2), it is possible to differentiate the kinds of tissue that are contained within it and their composition. The end product of this procedure is a highly detailed image of brain structure acquired in a 3 dimensional space where every voxel is usually set to be approximately 1 mm^3. Such scans can be employed to assess the grey matter (GM), white matter (WM) and CSF composition of each voxel in the image to allow its comparison between disease and control groups (Whitwell, 2009).

After having acquired an accurate anatomical representation of the participant's brain, other sequences can be employed to measure its function in a wide range of experimental conditions or specific structural characteristics.

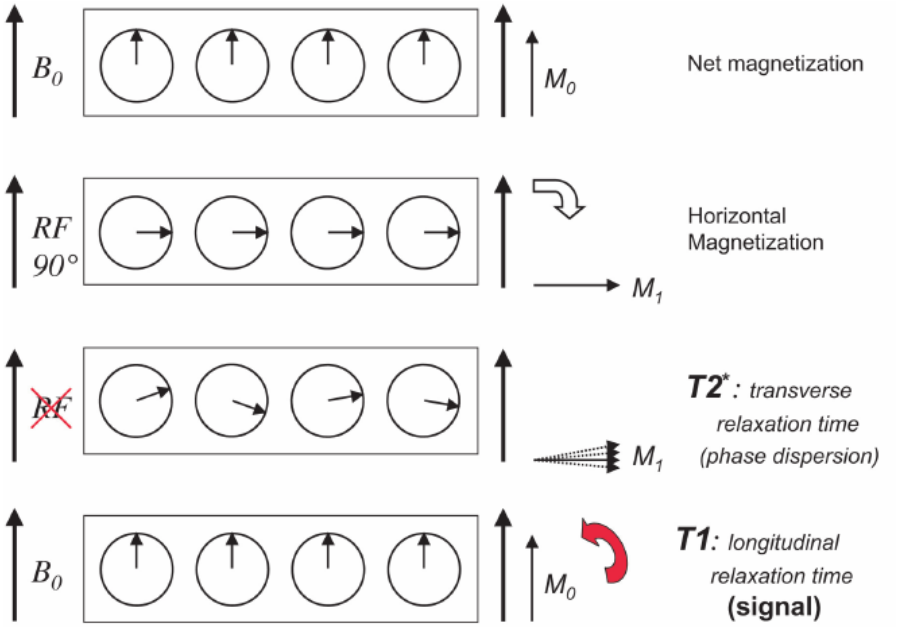

Figure 1 – In the presence of a static magnetic field (B_0), hidrogen nuclei align their spin parallel to the field. When they are exposed to a radiofrequency pulse (RF) at the Larmor frequency, their spins are shifted. When RF is removed, the spins tumble to their original alignment, allowing for measurement of T_1 and T_2*. Adapted from Tinaz and Stern, 2004.

3.3 FUNCTIONAL MAGNETIC RESONANCE

The technique of functional magnetic resonance imaging (fMRI) uses the same basic principles of MRI to evaluate the function of an organ or apparatus. In particular, neuronal fMRI is a technique that can evaluate the voxel-wise variations in blood flow in the brain and thus provide an indirect measurement of its activity.

In physiological brain tissue, local field inhomogeneities affect T_2 relaxation times, in which case the constant of the transverse signal decay is indicated with T_2*. This value is affected by the composition of the local blood supply (Logothetis and Wandell, 2004). In particular, deoxyhemoglobin (dHb) is paramagnetic (Pauling and Coryell, 1936) and influences the MR signal unlike oxygenated haemoglobin (Brooks et al., 1975). In the presence of dHb in red cells, the T_2 value decreases quadratically with field strength (Thulborn et al., 1982), but its effects on T_2* are even stronger (Ogawa et al., 1990). Therefore, by measuring T_2* in vivo, it is possible to selectively detect a signal that is affected by blood oxygenation blood oxygen dependent signal (BOLD).

Upon neural activation, cerebral blood flow is locally increased, compensating for the decrease in oxygen due to neuronal firing. This leads to the delivery of an oversupply of oxygenated blood and to an

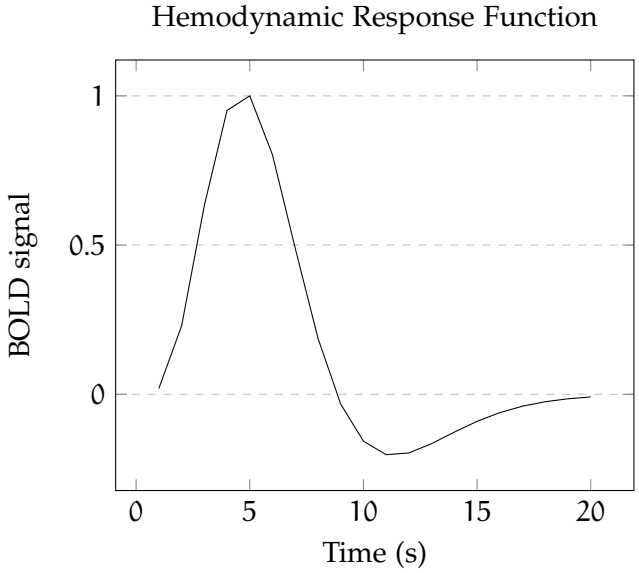

Figure 2 – An example of canonical hemodynamic response function. BOLD=blood oxygen dependent signal.

increase in the BOLD signal (Fox and Raichle, 1986; Fox et al., 1988). To capture this increment, brain volumes are usually acquired with a voxel size of 2-4 mm^3. The increased voxel size in comparison to anatomical scans allows to acquire a complete 3D image of the brain in around 2 seconds, which is sufficient to detect the BOLD response.

During most fMRI experiments, stimuli are delivered to the participant at known time points during the acquisition. The BOLD signal following each experimental event is then compared to a canonical hemodynamic response function (HRF) (Figure 2), a model curve that has been shown to be related to increased neuronal activity in brain regions (Attwell and Iadecola, 2002). By analysing the goodness of fit of the theoretical HRF model and the actual measured haemodynamic responses, it is possible to infer the variations of neural activity following the chosen stimuli in each voxel of the whole brain (Glover, 1999).

It is worth noting, however, that delivery of a stimulus is not always necessary in fMRI studies: many experiments nowadays are conducted in what is defined as "resting state", in which the patient simply lies in the scanner with his eyes closed and is not involved in any kind of task (Biswal et al., 1995; Lowe, Mock, and Sorenson, 1998; Cordes et al., 2000).

Diffusion weighted MRI allows the mapping of axon bundles in brain tissue in vivo (Jones, Knösche, and Turner, 2013; Behrens et al., 2003; Jones, 2010; Le Bihan et al., 1986; Le Bihan and Breton, 1985).

This is achieved by measuring the dephasing of protons' spins in the presence of a spatially-varying magnetic field ("gradient"). Depending on the direction of the gradient, nuclear spins will be displaced and their Larmor frequency will be changed. The longer the protons are allowed to diffuse, the higher the mean squared displacement per unit time of the water molecules in the tissue and the more molecules will distribute at different distances from their origin. By comparing the signal with and without the diffusion gradient applied, the portion of dephasing resulting from motion during the application of the gradient can be isolated. This depends on: the distribution of displacements during the diffusion time along the axis of the applied gradient, its strength and duration. Since diffusion time, gradient duration and strength are all known, it is possible to obtain a correlate for the motion of diffusing particles along a particular axis in space depending on tissue characteristics (Le Bihan and Breton, 1985).

By measuring the diffusion-induced dephasing along several axes using the same gradient strength, it is possible to estimate the diffusion of hydrogen nuclei in any number of directions whose "tips" lie on the surface of a sphere (Jones, Knösche, and Turner, 2013). This measurement reflects the general mobility of water and depends on temperature, viscosity, presence of large molecules, and, more interestingly, obstacles that water might encounter on its path such as cell membranes, myelin sheaths and microtubules. Such barriers slow down or even restrict the movement of diffusing particles (Beaulieu, 2002).

An ellipsoid can then be estimated for each voxel in the image (tensor), whose main eigenvector is the fastest diffusion direction. These tensors practically represent an surface of diffusion probability along several direction for the hydrogen nuclei within a voxel (O'Donnell and Westin, 2011).

Based on the tensor properties, it is possible to calculate voxel-wise diffusion indexes, such as fractional anisotropy (FA), axial, radial and mean diffusivity (MD). FA measures the fraction of anisotropic diffusion, which can be thought of as the difference of the tensor el-

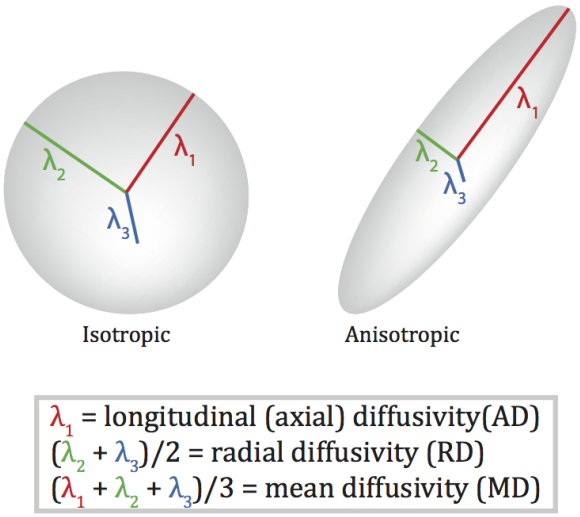

Figure 3 – Based on the main tensor eigenvectors (λ) it is possible to obtain measures of anisotropy, axial, radial and mean diffusivity from each voxel in the image. Figure adapted from Tromp, D., 2012.

lipsoid's shape from that of a perfect sphere. Directional diffusivity measures are obtained by averaging the tensor eigenvectors along different axes (Figure 3).

Voxelwise diffusivity measures are often compared between participant groups, since they are influenced by a wide number of tissue microstructural properties, such as the density, orientation and permeability of axons. Furthermore, tensor properties can be employed to reconstruct continuous fiber pathways and assess structural connectivity between brain regions (Mori and van Zijl, 2002; Mori et al., 1999; Tournier, Mori, and Leemans, 2011).

3.5 CONCLUSION

MRI is a safe and non-invasive technique that allows the investigation of the brain in vivo by using powerful magnetic fields.

In particular, by employing tailored sequences, it is possible to investigate tissue composition of different brain areas, as well as changes in their blood flow after stimulus delivery or at rest.

Finally, the path of axons and white matter fibre bundles can be characterized to map structural connections between different brain regions.

4

MAGNETIC RESONANCE IMAGING OF DEPRESSION

Magnetic resonance imaging has been employed for many years to try and investigate MDD pathogenesis and locate biomarkers that could prove useful in the clinic. Since it is safe and non-invasive, it has proven invaluable in understanding the alterations of brain structure and function associated with the disease in vivo.

4.1 STRUCTURAL MAGNETIC RESONANCE AND DEPRESSION

Recent meta-analyses of structural imaging studies have detected volumetric changes in several brain regions in MDD relative to controls. The most robust finding in the literature was reduced hippocampal volume in patients (Arnone et al., 2012; Campbell and MacQueen, 2004; Kempton et al., 2011; Schmaal et al., 2016; Videbech and Ravnkilde, 2004), but some reports have also highlighted a decrease in the volume of dorsolateral prefrontal, dorsomedial prefrontal, orbitofrontal cortex (OFC) and cingulate cortices, striatum and amygdala (Arnone et al., 2012; Bora et al., 2012; Lai, 2013; Sacher et al., 2012; Kempton et al., 2011). All of these regions are of key importance in regulating emotional responses and behaviour (Drevets, Savitz, and Trimble, 2008; Ongür, Ferry, and Price, 2003; Frodl et al., 2010a; Frank et al., 2014).

Involvement of the hippocampus in MDD, in particular, has been highlighted by several converging findings (see MacQueen and Frodl, 2011 for a review). Firstly, compatibly with the inflammatory hypothesis of the disorder, in this region stress has been shown to reduce neurogenesis (Thomas, Hotsenpiller, and Peterson, 2007; Pham et al., 2003) and cell proliferation (Malberg and Duman, 2003; Sapolsky et al., 1990). Indeed, conditions of chronic hypercortisolemia, such as Cushing's syndrome are associated with hippocampal atrophy that is reversible following normalization of cortisol levels (Starkman et al., 1999). In a clinical study, smaller hippocampi in MDD patients have also been found to be associated with increased markers of glucocorticoid receptor activation in peripheral plasma (Frodl et al., 2012).

Furthermore, depression is characterized by impaired encoding and retrieval from episodic memory, both of which are heavily dependent on this structure (Zakzanis, Leach, and Kaplan, 1998). Finally, hippocampal neurons project to prefrontal cortical regions as well as to the amygdala, on which they have a regulatory effect (Miller et al., 2010).

Although hippocampal volume loss might be dependent on patient age and disease duration (McKinnon et al., 2009; Schmaal et al., 2016), a meta-analysis of studies in first episode patients revealed significant hippocampal volume reductions, suggesting that smaller hippocampi may be a possible risk factor for depression, rather than a marker of disease progression (Cole et al., 2011). This is in agreement with longitudinal studies, which reported no significant hippocampal reduction in patients, but did show that smaller baseline hippocampus was associated with poorer clinical outcome (Frodl et al., 2008) and treatment response (Fu, Steiner, and Costafreda, 2013).

Evidence also suggests that antidepressant treatment (Frodl et al., 2008) and electroconvulsive therapy might induce an increase in hippocampal volume (Abbott et al., 2014) and that effects of antidepressants might be mediated by increased neurogenesis in the hippocampus (Duman, Nakagawa, and Malberg, 2001; Santarelli et al., 2003).

Another prominent finding in depressed patients is the reduction in gray matter in the subgenual anterior cingulate cortex (ACC) (Price and Drevets, 2009; Botteron et al., 2002; Coryell et al., 2005; Drevets et al., 1997; Hirayasu et al., 1999; Koo et al., 2008). This reduction has been even observed in young adults at high familial risk for MDD (Botteron et al., 2002; Hirayasu et al., 1999; Boes et al., 2008) and has been shown to worsen in time in subjects with psychotic mood disorders (Koo et al., 2008). This deficit seems to be common across unipolar and bipolar depression, even in the presence of psychosis (Hirayasu et al., 1999; Coryell et al., 2005; Adler et al., 2007; Haznedar et al., 2005). In MDD the reduction in subgenual anterior cingulate cortex (sgACC) volume persists despite successful treatment with antidepressant drugs (Drevets et al., 1997), but chronic lithium medication, which exerts robust neurotrophic effects in animal models, has been associated with an increase in gray matter volume in treatment responders in this and other prefrontal areas (Moore et al., 2009; Drevets, Savitz, and Trimble, 2008).

By using fMRI, several studies have detected significant differences between BOLD activity in MDD patients and healthy controls, both during tasks and in the resting state (see Fitzgerald et al., 2008; Groenewold et al., 2013 for metanalyses and Rive et al., 2013 for a review).

Tasks involving the emotional evaluation of stimuli as well as their cognitive processing have especially been conducted, since they provide an effective model of some hallmark features of MDD: the inability to shift attention away from the emotional content of a stimulus and the tendency to judge neutral or positive stimuli as negative (Gotlib and Joormann, 2010; Mathews and MacLeod, 2005).

Overall, emotional processing involves a network comprising several brain regions, organised in ventral and dorsal systems (Phillips et al., 2003b; Phillips et al., 2003a; Phillips, Ladouceur, and Drevets, 2008). The ventral system includes the amygdala, insula, ventral striatum, the ventral portion of the anterior cingulate gyrus and the medial OFC. These areas are especially important to identify the emotional significance of a stimulus and to produce an affective state in response to it. The dorsal system, on the other hand, regulates the produced affective state. It includes the hippocampus, the dorsal anterior cingulate gyrus and dorsal prefrontal cortex (Phillips et al., 2003b; Phillips et al., 2003a; Phillips, Ladouceur, and Drevets, 2008).

In depressed patients, areas belonging to the ventral system appear to be overactive during induction of negative emotions and hypoactive during that of positive ones (Fitzgerald et al., 2008; Groenewold et al., 2013). In particular, the amygdala and striatum have shown these pattern consistently and have been part of models describing the neural correlates of emotional dysfunction in depression for a long time (Leppänen, 2006; Phillips et al., 2003b).

The amygdala is involved in directing attention to both positive and negative stimuli, in generating a congruous emotional response to them and in prioritizing their processing in other brain areas (Pessoa and Adolphs, 2010; Costafreda et al., 2008; Murray, 2007; Jacobs et al., 2012; Sander, Grafman, and Zalla, 2003). The ventral striatum, on the other hand, receives input from and interacts with the amygdala, but constitutes a central part of the reward circuit and is more often involved in the processing of positive emotions (Haber and Knutson, 2010). Stronger activation for negative stimuli and weaker activation for positive ones in these structures might represent a neural correlate

of the deficits of MDD patients in directing attention away from negative stimuli and in negative interpretation of positive stimuli (Elliott et al., 2002; Harmer, Goodwin, and Cowen, 2009; Roiser, Elliott, and Sahakian, 2012; Gotlib and Joormann, 2010; Mathews and MacLeod, 2005). The dorsal ACC also showed an increased response to negative emotions and reduced activation to the positive ones (Groenewold et al., 2013). This has led to the suggestion that this region might act as a link between the frontal and subcortical areas (Mayberg et al., 1997).

Concerning regions belonging to the dorsal system, these have mostly shown a lack of activation in response to negative emotional stimuli in depressed patients (Fitzgerald et al., 2008; Groenewold et al., 2013). The dorsal prefrontal cortex, in particular, is critical for top-down modulation of both positive and negative emotional responses (Drevets, 1999; Drevets, 2007; Drevets, Savitz, and Trimble, 2008) and its reduced activation in MDD has been shown consistently across several studies (Fitzgerald et al., 2008). It has also been postulated for a long time that a deficit of lateral prefrontal regions might be involved in the cognitive symptoms of the disorder (Dolan et al., 1993), as they are more active in healthy controls during working memory, word generation and planning tasks in which depressed patients show poorer performance (Murrough et al., 2011).

In addition to the findings relating to the ventral and dorsal systems, some studies also reported significant differences between patients and controls in the superior temporal lobe, with negative stimuli producing increased activation in this area and positive ones producing a reduced one (Fitzgerald et al., 2008; Groenewold et al., 2013). The superior temporal gyrus plays an important role in emotional regulation and social cognition (Allison, Puce, and McCarthy, 2000; Gallagher and Frith, 2003; Lévesque et al., 2003; Olson, Plotzker, and Ezzyat, 2007) and its volume has been found to be reduced in depressed patients proportionally to symptom severity (Takahashi et al., 2010).

Finally, posterior cingulate cortex hyperactivity has been shown as well in response to both positive and negative images in MDD patients (Fitzgerald et al., 2008). It has been suggested that this region is involved in self assessment and elaboration of emotional content arising from visual input (George et al., 1995; Vogt, Berger, and Derbyshire, 2003; Vogt, Vogt, and Laureys, 2006) and its differential activation in MDD patients might indicate an alteration of how these stimuli are

processed. Also, this region is a part of the dorsal default mode network (DMN), a set of regions known to be active in the resting state and to reduce their activation during tasks (Raichle et al., 2001).

Differences in activity in the DMN in MDD patients in response to emotional content have been reported in the past (Grimm et al., 2008). It is unclear, however, whether this finding truly indicates a reduced deactivation of the network during the task or rather a permanently increased abnormal resting state activity and a lack of its deactivation during emotional processing. In line with the latter hypothesis, Sheline et al., 2009 reported a specific failure in decreasing DMN activity in depressed patients in response to negative emotional pictures. DMN regions are thought to be involved in self-inspection and monitoring of the internal and external milieu (Buckner, Andrews-Hanna, and Schacter, 2008; Gusnard et al., 2001; Raichle et al., 2001) and these are processes that may be overactive in depression, especially in the form of ruminations (Ray et al., 2005).

To sum up, brain function in major depressive disorder seems to be associated with hyperactivity during negative affect in ventral prefrontal regions such as the cingulate cortex and in subcortical areas belonging to the limbic system like the insula and hippocampus. The dorsolateral prefrontal cortex shows hypoactivity in the same condition, possibly hinting at a deficit of top-down control on affect generation. Exposure to positive emotional stimuli showed opposite patterns of activation (Figure 4). Differences in regions involved in reward processing, such as the ventral striatum, have been observed as well. Finally, there is increasing evidence of Default Mode Network hyperactivity in the disease, which might be involved in the pathogenesis of ruminations.

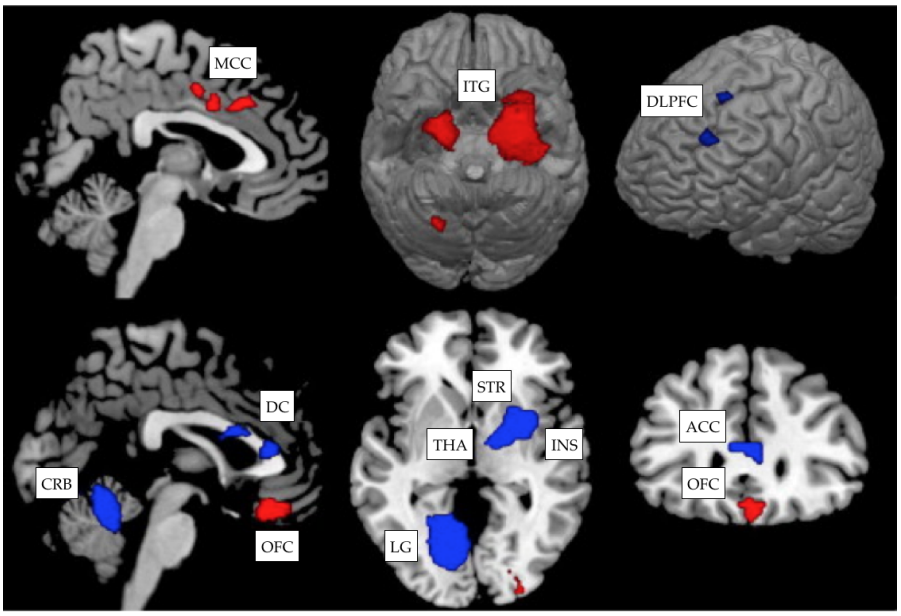

Figure 4 – Group differences in activation during emotional processing studies in the latest meta-analysis. Top row: negative emotions, bottom row: positive emotions. Red=MDD>HC, blue=HC>MDD. While processing negative emotions, patients show greater activation of the middle cingulate cortex (MCC) and inferior temporal gyrus (IFG) as well as reduced left dorsal prefrontal (DLPFC) activations. Positive emotions elicit increased activation in patients in the orbitofrontal cortices (OFC) and decreased activation in the anterior cingulate cortex (ACC), dorsal cingulate (DC), cerebellum (CRB), insula (INS), striatum (STR) and thalamus (THA), and left lingual gyrus (LG). Results corrected at $p_{FDR}<0.05$, MNI space. MDD=depressed patients, HC=healthy controls, FDR=false detection rate. Adapted from Groenewold et al., 2013.

4.3 DIFFUSION MAGNETIC RESONANCE

A recent meta-analysis (Liao et al., 2013) has shown that MDD patients have consistently decreased prefrontal and temporal cortical FA in specific areas, which might be related to changes in axon directionality and density both in late life depression (Alexopoulos et al., 2002; Taylor et al., 2004; Nobuhara et al., 2006; Yang et al., 2007) and young adults with first disease onset (Li et al., 2007; Ma et al., 2007). In particular, the fiber tracts affected include the inter-hemispheric fibres running through the genu and body of the corpus callosum, the right inferior longitudinal fasciculus, right posterior thalamic radiation and the right inferior fronto-occipital fasciculus (Figure 5).

The fibre bundles belonging to the genu and body of the corpus callosum seem to be particularly affected (Liao et al., 2013) and this finding is consistent with that of two other recent meta-analyses (Chen et al., 2016; Wise et al., 2016). As a whole, these studies suggest that im-

paired prefrontal interhemispheric structural connectivity might be of key importance in affective disorders. Indeed, as previously described, midline perfrontal areas such as the medial prefrontal cortex and the ACC are central to the current hypotheses on the circuits involved in mood dysregulation and depression (Phillips, Ladouceur, and Drevets, 2008; Wise et al., 2014).

The inferior longitudinal fasciculus is an associative bundle connecting the occipital and temporal lobes. These long fibres connect visual areas to the amygdala and hippocampus (Catani et al., 2003). This tract is involved in face recognition (Fox, Iaria, and Barton, 2008), visual perception (Ffytche, 2008), reading (Epelbaum et al., 2008), recognition of facial emotion (Kleinhans et al., 2008) and other functions related to language (Vadnal, Parthasarathy, and Parthasarathy, 2012). In depressed subjects this tract, besides showing reduced FA, shows hyperintensity compared to controls (Sheline et al., 2008). White matter lesions in the inferior longitudinal fasciculus might interrupt connections between the occipital cortex and the medial temporal structures, amygdala, hippocampus, and parahippocampus (Catani et al., 2003). This might lead to affective valence signals not being normally transmitted (Sheline et al., 2008).

Similarly, the inferior fronto-occipital fasciculus is a ventral associative bundle connecting the ventral occipital lobe and the OFC (Catani, 2007). This tract has a role in emotional visual perception (Catani et al., 2002) and alterations in this process as well as reduced FA in the tract have been observed in depression (Cullen et al., 2010; Kieseppä et al., 2010). Interestingly, a reduction in FA values in these tracts in adolescents at high familial risk for depression before the clinical manifestation of illness was observed, suggesting that reduced FA might be a vulnerability marker for the disorder (Huang et al., 2011).

The thalamic radiations are connections between the thalamus and most regions of the cortex, forming a major part of the internal capsule and corona radiata (Liao et al., 2013). The anterior portion of the internal capsula has been used as a target in deep brain stimulation for treatment-resistant depression, although the mechanisms through which this clinical practice achieves its results are unclear (Malone et al., 2009). It is possible that stimulation in this region might induce positive affective changes by activating the brain dopaminergic reward system and frontal lobe emotional processing areas (Coenen et al., 2011; Coenen et al., 2012).

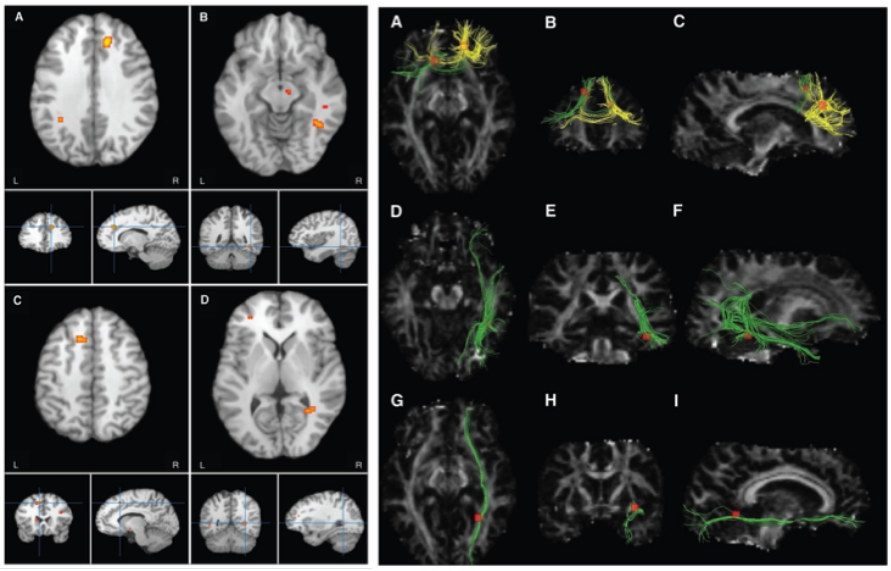

Figure 5 – Left: Decreases in fractional anisotropy were localized in the (A) white matter of the right frontal lobe, (B) right temporal lobe, (C) left frontal lobe and the (D) right occipital lobe. Right: Fascicles traversing the right and left frontal regions were the genu and the body of the corpus callosum (A, B, C). Fascicles traversing the right fusiform gyrus were the right inferior longitudinal fasciculus, interior fronto-occipital fasciculus and posterior thalamic radiation (D, E, F). Fascicles traversing the right occipital region were the right inferior fronto-occipital fasciculus (G, H, I). Adapted from Liao et al., 2013.

4.4 CONCLUSIONS

MDD patients show volume reduction and grey matter loss in regions that are crucial for emotional regulation, in particular the hippocampus and ACC (Arnone et al., 2012).

The function of emotional processing circuits is also affected in depression: areas that are responsible for the generation of negative emotional responses such as the amygdala are hyperactive, whereas those involved in inhibitory top-down regulation, such as the dorsolateral prefrontal cortex, are hypoactive (Groenewold et al., 2013).

Finally, fibre tracts connecting emotional processing areas with each other and with primary sensory regions also show structural alterations (Liao et al., 2013).

5

MAGNETIC RESONANCE IMAGING OF DEPRESSION GENETICS

Throughout the years, several studies have investigated the effect of allelic variants in functional polymorphisms associated with MDD on brain structure and function (see Savitz and Drevets, 2009 and Won and Ham, 2016 for reviews).

5.1 MONOAMINES

5.1.1 *Monoamine oxidase*

As previously outlined, a VNTR of the MAOA gene has been found to be associated with depression, especially in females, in particular in its low activity variant (Schulze et al., 2000).

Healthy individuals carrying the high risk allele of this region showed a significant volume reduction both in the amygdala (Meyer-Lindenberg and Weinberger, 2006) and in the entire cingulate gyrus, particularly in the ACC (Meyer-Lindenberg and Weinberger, 2006). Some studies found increased OFC volume in controls with the high-functioning variant of the gene (Meyer-Lindenberg and Weinberger, 2006; Cerasa et al., 2010), but volume reduction in this region was also reported (Cerasa et al., 2008).

Carriers of the high-risk variant of the VNTR also had increased hippocampal activation compared to other genotypes during the retrieval of negative emotional material (Meyer-Lindenberg and Weinberger, 2006) and presentation of emotional faces (Lee et al., 2008). Similarly, they exhibited increased amygdala and ACC activation during anger control (Denson et al., 2014). This hyperactivation was then followed by an increased functional coupling between the amygdala and dorsal ACC following the challenge, which was absent in participants carrying the low-risk polymorphism (Denson et al., 2014). Finally, healthy individuals with the low-functioning variant of the gene showed increased functional coupling between the amygdala and venteromedial prefrontal cortex (VMPFC) (Buckholtz et al., 2007), whereas MDD patients carrying the high functioning polymorphism

showed reduced amygdala–dorsal ACC connectivity (Dannlowski et al., 2009).

5.1.2 *Tryptophan hydroxylase*

Among healthy controls, carriers of a T allele in the rs4570625 SNP of *TPH2* showed a significantly smaller hippocampal volume (Inoue et al., 2010). Healthy G allele homozygotes, on the other hand, showed significantly lower gray matter concentration in the inferior OFC compared to T allele carriers (Yoon et al., 2012).

The T allele of the SNP was associated with greater amygdala activation in response to emotional faces in a study (Canli et al., 2005). However, another experiment conducted on an Asian population reported an opposite effect, with G allele homozygotes showing the highest activation in response to sad facial stimuli and the T allele homozygotes showing the lowest activation response (Lee et al., 2008).

5.1.3 *Serotonin transporter*

The long and short variants of 5-HTTLPR have been extensively studied. MDD patients who are homozygous for the long variant of the allele show significantly reduced bilateral hippocampal volumes compared to patients homozygous for the short allele. However, healthy controls carrying the homozygous s variant also show reduced hippocampal volume compared to those carrying the l variant (Frodl et al., 2004; Frodl et al., 2008).

A possible explanation for these conflicting findings might lie in environmental variables: patients who carry the s allele and have a history of emotional neglect develop smaller hippocampal volumes, compared to those who only have either an environmental or a genetic risk factor (Frodl et al., 2010a). In line with this result, other studies investigating 5-HTTLPR have shown that the hippocampi of s allele carriers seem to be especially susceptible to an adverse environment (Rabl et al., 2014). In adolescents, increasing copies of this variant were also found to predict smaller hippocampal volume and increased risk of developing MDD (Little et al., 2014).

Gender was also reported to influence 5-HTTLPR effects on hippocampal volumes. Price et al., 2013 investigated healthy individuals showing depressive symptoms: female s allele carriers had larger hip-

pocampal volumes, whereas males carrying the same genetic variant had smaller volumes.

Regarding amygdala volume, findings are still inconclusive: healthy s allele carriers showed a significant reduction in amygdala volume (Pezawas and Meyer-Lindenberg, 2010), but another study found s allele homozygous healthy individuals with subclinical anxiety to have a larger amygdala volume (Cerasa et al., 2014).

In the ACC, particularly its subgenual portion (Pezawas et al., 2005), healthy individuals carrying the s allele exhibited reduced gray matter density (Canli et al., 2005; Frodl et al., 2008). The presence of the s allele also predicted smaller medial OFC volumes in a sample of adolescents (Little et al., 2014).

Concerning modifications of brain functions, amygdala responses were faster (Furman et al., 2011) and greater in healthy subjects who carried the s allele during a wide variety of tasks, such as matching fearful and angry facial expressions (Hariri et al., 2002; Hariri et al., 2005), recovering from induced sad mood (Gillihan et al., 2010), exposure to negative words (Canli et al., 2005), threats (Bertolino et al., 2005), masked emotional faces (Dannlowski et al., 2007), aversive pictures (Heinz et al., 2005) and sad faces (Dannlowski et al., 2010).

In MDD patients specifically, similarly to what was observed in controls, s allele carriers had increased amygdala activation in response to emotional faces (Dannlowski et al., 2007). This amygdalar hyper-reactivity was especially present in chronic patients, which suggests that 5-HTTLPR variants might influence disease duration (Dannlowski et al., 2008). Another study investigated a group composed of MDD patients and healthy controls using a similar task, once again confirming that s allele carriers showed a greater amygdala response regardless of diagnosis (Costafreda et al., 2013).

Overall, current findings point towards an effect of 5-HTTLPR polymorphisms on amygdalar responses. Meta-analyses on both healthy and psychiatric populations confirmed this effect, that may account for up to 10% of variable amygdala response (Munafò, Brown, and Hariri, 2008; Murphy et al., 2013).

5-HTTLPR polymorphisms were also shown to affect coupling between the prefrontal cortex and amygdala. Participants carrying the s allele showed greater functional connectivity between the two structures (Friedel et al., 2009; Pezawas et al., 2005; Heinz et al., 2005) and reduced connectivity between the amygdala and ACC (Pezawas et al., 2005; Costafreda et al., 2013).

5.1.4 *Serotonin receptor*

Differences in amygdala reactivity were associated with 5-HTT1A receptor density (Fisher et al., 2006), prompting the study of its functional rs6295 polymorphism. G allele carriers, compared with C homozygotes, showed increased amygdala activity in response to emotional faces (Dannlowski et al., 2007) and decreased threat-related reactivity of this structure (Fakra et al., 2009). These findings, however, could not be replicated (Lee et al., 2008).

5.1.5 *Noradrenaline*

Only one study so far investigated the relationship between a polymorphism of the noradrenaline transporter gene and morphological brain abnormalities in MDD patients (Ueda et al., 2016). Specifically, the Authors report an interaction effect between diagnosis and genotype, with the high-risk allele being associated with a reduced grey matter concentration in the dorsolateral prefrontal cortex in first episode drug-naïve patients compared to controls with the same genotype.

5.1.6 *Dopamine*

Polymorphisms in the VNTR of the dopamine transporter gene have been associated with differences in midbrain activation during memory encoding of visual stimuli (Schott et al., 2006). However, no studies have been conducted so far to investigate these effects in MDD patients.

5.2 BRAIN-DERIVED NEUROTROPHIC FACTOR

The met allele of a common functional SNP of BDNF is associated with smaller hippocampal volume whether they are healthy controls (Pezawas et al., 2004) or belong to various clinical populations including depressed, schizophrenics and bipolar patients (Pezawas et al., 2004; Bueller et al., 2006; Ho et al., 2006; Takahashi et al., 2008; Chepenik et al., 2008; Frodl et al., 2007). Concerning healthy people, the effect of this polymorphism seems to be present especially if they are exposed to stress (Gatt et al., 2009) or suffering from high level of neuroticism (Joffe et al., 2009).

The same variant has been shown to be associated with higher amygdala reactivity in controls (Montag et al., 2008).

5.3 FK506 BINDING PROTEIN 51

Some MRI studies have recently investigated grey matter volume, white matter integrity and neural responses to stimuli in patients carrying high-risk allele variants of the rs1360780 FKBP5 SNP, highlighting structural and functional differences in brain areas involved in emotional processing. Overall, in patients carrying the T (risk) FKBP5 alleles, compared to those without it, these studies found larger volumes in the amygdala and middle and inferior orbitofrontal gyri (Hirakawa et al., 2016) as well as smaller volumes in the dorsal ACC (Fujii et al., 2014).

In these participants, white matter integrity was also found to be altered in the dorsal ACC, posterior cingulum (Fujii et al., 2014; Tozzi et al., 2015; Fani et al., 2014), insula and inferior frontal gyrus (Tozzi et al., 2015).

Functional studies showed higher BOLD responses in the amygdala during an emotional face matching task in participants carrying the high risk allele (Holz et al., 2014), which were also influenced by exposure to childhood trauma (White et al., 2012).

5.4 CONCLUSIONS

Most studies have shown that polymorphisms associated with MDD involve altered responses and structural abnormalities in brain structures involved in emotional processing, in particular the amygdala, hippocampus and orbitofrontal cortex (Savitz and Drevets, 2009).

So far, investigations in this regards have met with several challenges. In particular, sample sizes for imaging studies are usually low and have therefore difficulties in detecting the small effect sizes of polymorphic variants. Furthermore, even if overall heritability of MDD is high, individual polymorphisms are expected to explain only minor portions of it, so that all high-risk variants should be simultaneously considered (Hashimoto et al., 2015).

Currently, the establishment of large-scale imaging collaborative networks such as the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium has the goal of overcoming

these challenges to provide reliable results on a global scale (Thompson et al., 2014).

6

HYPOTHESIS

Overall, from the literature presented it appears clear that no individual gene can alone explain the symptoms or etiology of MDD. However, it is possible that variants in specific genes might represent vulnerability factors that coupled with environmental cues can lead to depressive symptoms.

Several studies have shown that childhood adversity can be an especially strong predictor of MDD later in life (Kessler, Davis, and Kendler, 1997; Heim et al., 1997; Heim, Plotsky, and Nemeroff, 2004; Teicher et al., 2009; Teicher et al., 2006; Widom, DuMont, and Czaja, 2007). This has been reported for different types of stressors, including trauma, adverse events, neglect, aggression as well as physical abuse (Kessler, Davis, and Kendler, 1997; Rubino et al., 2009; Teicher et al., 2006; De Marco, 2000; Widom, DuMont, and Czaja, 2007; Angst et al., 2011; Sugaya et al., 2012).

It is still unclear how exactly adverse experiences might have this effect, but they have been shown to be associated with structural abnormalities in specific brain regions, for whose development early life might be an especially critical time (Andersen, n.d.; Andersen and Teicher, 2008; Andersen and Teicher, 2008; Frodl et al., 2016).

Interestingly, chronic stress during childhood also chronically dysregulates the HPAA (Weiss, Longhurst, and Mazure, 1999; Paus, Keshavan, and Giedd, 2008; Kaufman and Charney, 2001; Heim et al., 1997).

The aim of our project was to investigate how genetic predisposition and childhood adversity might interact to explain structural and functional brain abnormalities in MDD patients. We expected participants with high-risk genetic variants to be more vulnerable to the effects of an adverse environment during childhood. Therefore, the combination of these two factors should bring about changes that would otherwise be undetectable in brain regions associated with emotional processing and regulation.

As a marker of genetic vulnerability, we chose to focus on the FKBP5 gene, which shows the rs1360780 functional polymorphisms that increases MDD risk (see Chapters 2 and 5). Studies assessing the interaction of high-risk SNPs with environmental stressors have shown

significant results, albeit with small effect sizes (Klengel et al., 2013). This is also the case of other polymorphisms, such as the ones of 5-HTTLPR, but FKBP5 is directly involved in glucocorticoid receptor regulation (Grad and Picard, 2007; Pratt and Toft, 1997) and is therefore an ideal candidate to explore this interaction, since the effects of childhood adversity on brain structure and function are thought to be stress-mediated.

First of all, we investigated which functional changes were associated with MDD in an fMRI task involving directing attention towards and away from the valence of emotional stimuli, which had been previously published by our group (Lisiecka et al., 2012). Recent findings suggest that brain processes involved in MDD symptomatology might include a wide array of regions, especially those belonging to the ventral and dorsal emotion processing networks (Okon-Singer et al., 2015). During our task, we expected to detect a higher coupling of ventral regions while participants were focusing on the valence of pictures shown. While they were trying to ignore their emotional content, on the other hand, we expected an involvement of dorsal prefrontal regions. We also hypothesised altered activations and functional connectivity between these structures in MDD patients compared to controls. This study was published on "Journal of Affective Disorders" (Tozzi et al., 2017) and is described in Chapter 11.

Secondly, we investigated whether patients carrying the high-risk allele of the rs1360780 FKBP5 functional SNP showed differential activation during our task conditions compared to patients without genetic risk. We then sought to determine if these changes were mirrored by structural modifications in the white matter similarly to what was reported by other studies (Fani et al., 2014). Finally, we tested whether they could be explained by the interaction between genetic risk and exposure to childhood trauma. We expected early life adversity and genetic risk to interact and produce structural changes, affecting areas functionally involved in the disorder symptoms and showing the strongest effect in patients with both risk factors. This work was published in "Neuropsychopharmacology" (Tozzi et al., 2015) and is laid out in Chapter 12.

Finally, we investigated epigenetic modifications of the FKBP5 gene in depressed patients and controls. Previous studies have hypothesised that chronic stress might functionally regulate *FKBP5* by methylation of its regulatory sites (Tyrka, Ridout, and Parade, 2016; Provencal and Binder, 2015). We tested whether this modification was re-

lated to childhood adversity as well as to reduced grey matter and altered function in emotional control areas. We expected a lower *FKBP5* methylation to be associated with reduced grey matter and altered activity in these regions. This last analysis is was published in "Neuropsychopharmacology" (Tozzi et al., 2017) and is presented in Chapter 13.

Part II

MATERIALS AND METHODS

7

PARTICIPANTS

One of the main focuses of our work was to expand a previously existing database of 54 MDD patients and 53 healthy controls (HC), collected between June 2009 and February 2011. Imaging data acquisition for these participants had been conducted at the centre for advanced medical imaging (CAMI) at St. James' Hospital, therefore this dataset will be labelled "CAMI" from here on.

Forty five controls and 61 MDD patients were then subsequently recruited from December 2013 to January 2016, from which biological samples and brain scans were collected at the Trinity College institute of neuroscience (TCIN). From here on, this second dataset will be labelled "TCIN".

7.1 RECRUITMENT

For the recruitment material including study information, consent forms and scales see Appendix d.

The study was approved by the Research Ethics Committee for Tallaght & St. James's Hospital and was designed as well as performed in accordance to the ethical standards laid out by the Declaration of Helsinki.

Participants were recruited from the mental health services of the Adelaide and Meath Hospital, incorporating the National Children's Hospital and St. James's Hospital (CAMI dataset) or from the psychiatric outpatient clinic at Sheaf House in Tallaght Hospital and from the Mary Mercer Clinic, Jobstown, Dublin 24 (TCIN dataset). Any patient presenting with unipolar depression and currently suffering from a major depressive episode was considered for the study. Exclusion criteria were age <18 or >65, history of neurological or comorbid psychiatric disorders including alcohol or substance dependency (Axis I or Axis II), other severe medical illness, head injury or current substance abuse.

Psychiatrists and consultants in these sites were informed of the inclusion and exclusion criteria. After conducting a clinical interview

with a patient, if they considered them suitable for inclusion in the study, they referred them to the experimenter.

A detailed description of the study was then given to the patient and written informed consent was obtained if they decided to participate. Subsequently, an appointment was arranged at the experiment site. During the collection of the TCIN dataset, patients were also instructed on how to collect saliva samples during the day prior to the appointment and told to bring the samples with them.

Upon arrival to the site, inclusion and exclusion criteria were assessed again through a structured clinical interview for DSM disorders 1 (SCID-I). Demographic variables were recorded, including age, sex, marital status, years of education, ethnicity and body mass index (BMI). Education was standardised according to the European Qualifications Framework (EQF, https://ec.europa.eu/ploteus/en/content/descriptors-page) Scales were then administered (see Chapter 8) and a blood sample was collected. The participant was finally instructed on the fMRI task before being brought to the MRI facility for the scan, which was the last part of the experiment.

Healthy controls were recruited through advertisement on the Trinity College Campus and word of mouth. They were considered eligible if they had no prior history of mental illness, were medically healthy, and were not on any medications other than the oral contraceptive pill. Whenever the experimenter was contacted by a potential healthy control, the same procedure was followed as outlined above.

One control from the TCIN dataset had a sister and a cousin that were also used as controls for our studies.

For an overview of the demographic characteristics of the CAMI and TCIN samples, see Table 2.

	CAMI		Test (p)	TCIN		Test (p)
	HC	MDD		HC	MDD	
N	53	53		45	61	
Age (years)	36.42 ± 13.03	41.81 ± 10.76	t=-2.32 (0.02)	30.78 ± 10.77	35.39 ± 13.00	t=-1.94 (0.05)
Sex (F/M)	29/24	33/20	χ^2=0.43 (0.55)	30/15	39/22	χ^2=0.85 (0.84)
BMI	23.23 ± 3.26	25.62 ± 3.88	t=-3.32 (<0.01)	23.57 ± 3.78	27.08 ± 8.38	t=-2.49 (0.01)
Smoking (yes/no)	11/42	17/36	χ^2=1.74 (0.27)	5/40	23/38	χ^2=9.43 (<0.01)
Partnership (single/not single)	28/13	10/23	χ^2=10.56 (0.01)	28/17	36/24	χ^2=0.53 (0.84)
EQF	7 (2-8)	4.50 (1-7)	U=211.50 (<0.01)	7 (2-8)	4 (1-7)	U=508.50 (<0.01)
rs1360780 (CC/T*)	22/23	23/24	χ^2=0.10(0.95)	12/14	19/25	χ^2=2.50 (0.28)

Table 2 – Overview of demographics. Data from the Centre for Advanced Medical Imaging (CAMI) and Trinity College Institute of Neuroscience (TCIN) are shown. EQF was only available for 39 HC and 28 MDD from the CAMI dataset and from 47 HC and 59 MDD from the TCIN dataset. rs1360780 could be genotyped only for 45 HC and 47 MDD from the CAMI dataset and from 26 HC and 44 MDD from the TCIN dataset. For parametric variables, mean and standard deviation are given. For non-parametric variables, the median as well as minimum and maximum values are given. Statistical tests compare HC and MDD within each dataset. HC=healthy controls; MDD=depressed patients; BMI=body mass index, EQF=standardized years of education according to the European Qualifications Framework.

8

RATING SCALES

For the recruitment material including study information, consent forms and scales see Appendix d.

Self and observer rated scales were filled out for all participants included in the study. Rating scales were used to assess current symptom severity: the Hamilton depression scale (HAMD) (Hamilton, 1986), Beck depression inventory (BDI) (Beck et al., 1961) and Pittsburgh sleep quality index (PSQI) (Buysse et al., 1989). The childhood trauma questionnaire (CTQ) was used to investigate early life adversity (Bernstein, D. P and Fink, L., 1998).

8.1 HAMILTON DEPRESSION RATING SCALE

The Hamilton Depression Rating scale is a multiple item clinician-rated questionnaire used to provide an indication of depression severity in adults by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms (Hamilton, 1986).

The version of the scale used in the present study includes 17 items to be rated, and four other questions that are not rated but are used to provide additional clinical information. Each item on the questionnaire is scored on a 3 or 5 point scale depending on the item. A total score of 0-7 is considered normal and scores of 20 or higher indicate depression.

8.2 BECK'S DEPRESSION INVENTORY

The Beck's Depression Inventory is a multiple-choice self-report questionnaire to ensure the severity of depression. It is composed of items relating to symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex (Beck et al., 1961).

The version used in the present study is updated to a 1996 revision of the scale (Beck et al., 1996). It contains 21 items, each answer being

scored from 0 to 3. Standardized cutoffs used for depression severity using this scale are as follows: 0-13: minimal; 14-19: mild; 20-28: moderate; 29-63: severe.

8.3 PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index is a self-report questionnaire that assesses sleep quality over the month before administration. The measure consists of 19 individual items, creating 7 components that produce one global score. (Buysse et al., 1989).

Each item is weighted on a 0–3 interval scale. The component scores consist of subjective sleep quality, sleep latency (i.e. how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e. the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction due to lack of sleep. The global PSQI score is then calculated by summing the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality.

8.4 CHILDHOOD TRAUMA QUESTIONNAIRE

The Childhood Trauma Questionnaire is a screening tool for histories of abuse and neglect during childhood. The self-report measures 5 types of maltreatment: emotional, physical and sexual abuse as well as emotional and physical neglect. A three-item minimization-denial subscale is also included to check for extreme response bias, specifically attempts by respondents to minimize their childhood abuse experiences. (Bernstein, D. P and Fink, L., 1998).

The occurrence during his or her childhood of 28 items is rated by the participant on a 5-point Likert scale which ranges from "Never True" to "Very Often True". Scores from the items are then added according to the subscales, giving a score for each ranging from 5 (no history of abuse or neglect) to 25 (extreme history of abuse or neglect). A total score can also be obtained by adding all subscales (except the minimization-denial one) leading to a total range of 25 to 125.

An overview of the questionnaire data for the two datasets is presented in Table 3.

	CAMI		Test (p)	TCIN		Test (p)
	HC	MDD		HC	MDD	
N	53	53		45	61	
HAMD	2 (0-15)	28 (14-45)	U=2808 (<0.01)	0 (0-14)	23 (6-36)	U=2741 (0.01)
BDI	2 (0-24)	31 (3-59)	U=2773 (<0.01)	1 (0-13)	34 (0-53)	U=923 (<0.01)
PSQI	3 (0-15)	13 (4-20)	U=2585 (<0.01)	3 (0-9)	13 (4-19)	U=2295 (<0.01)
CTQ (total)	30 (25-52)	39 (25-104)	U=2091 (<0.01)	27 (25-53)	43 (25-88)	U=1972 (<0.01)
CTQ EA	6 (5-20)	8 (5-23)	U=1909.50 (<0.01)	5 (5-13)	10 (5-24)	U=1885.50 (<0.01)
CTQ PA	5 (5-11)	6 (5-25)	U=1840 (<0.01)	5 (5-11)	7 (5-20)	U=1659.50 (<0.01)
CTQ SA	5 (5-10)	5 (5-25)	U=1809 (<0.01)	5 (5-7)	5 (5-25)	U=1448 (<0.01)
CTQ EN	7 (5-16)	10 (5-25)	U=2061 (<0.01)	6 (5-13)	12 (5-21)	U=1913 (<0.01)
CTQ PN	5 (5-10)	7 (5-17)	U=1897.50 (<0.01)	5 (5-14)	6 (5-16)	U=1744 (<0.01)
CTQ MD	1 (0-3)	0 (0-3)	U=1179 (1.12)	0 (0-3)	0 (0-3)	U=1015.50 (0.03)
Medication (none/SSRI/SNRI/other)		14/16/16/7			17/25/11/6	
Illness duration (years)		12 (0.25-44)			4.42 (0-56)	

Table 3 – Overview of questionnaire scores and medication. Data from the Centre for Advanced Medical Imaging (CAMI) and Trinity College Institute of Neuroscience (TCIN) are shown. Statistical tests compare HC and MDD within each dataset. For non-parametric variables, the median as well as minimum and maximum values are given. HC=healthy controls; MDD=depressed patients; HAMD=Hamilton depression rating scale; BDI=Beck depression inventory; PSQI=Pittsburgh sleep quality index; CTQ=childhood trauma questionnaire; EA=emotional abuse; PA=physical abuse; SA=sexual abuse; EN=emotional neglect; PN=physical neglect; MD-minimization/denial; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin norepinephrin reuptake inhibitors; other=anti-psychotic, gabapentin or agomelatine

9 BIOLOGICAL SAMPLES

For each participant, blood samples were collected, to assess inflammatory profile and HPAA genetics.

Inflammatory markers were analyzed in the Trinity College Institute of Neuroscience under the supervision of Prof. Veronica O'Keane and Prof. Andrew Harkin. Results of these analyses are beyond the scope of the current work and will not be presented.

Genetic polymorphisms of *FKBP5* were assessed through a collaboration between Prof. Frodl and the Department of Genetics of Trinity College Dublin (Dr. Derek Morris, Prof. Michael Gill). Methylation of the intron sites of the gene was investigated through a collaboration with the University of Montreal, Canada (Dr. Linda Booij).

9.1 PAXGENE WHOLE BLOOD

Collection of 2.5 ml of blood was performed into PAXgene DNA tubes. Filled PAXgene tubes were stored at room temperature (20°C) for 48 hours, moved to -20°C for 48 hours and finally to -80°C in order to gradually reduce temperature. Labelled tubes were stored at -80°C until DNA extraction was performed.

9.2 FKBP5 POLYMORPHISM

rs1360780 was genotyped from blood in this sample using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping was >95% and all samples were in Hardy-Weinberg equilibrium ($p>0.05$). Along with the test samples, a number of HapMap CEU DNA sample positive controls (www.hapmap.org) and non-template negative controls were genotyped for quality control purposes. For positive controls, all genotypes were found to be concordant with available online HapMapdata.

Genomic DNA was extracted from whole blood samples, which had been collected into PAXgene Blood DNA Tubes (IVD) using the Flexigene DNA Blood Kit (Qiagen) following the manufacturer's recommended protocol.

DNA quantity and quality was assessed using the NanoDrop 2000 spectrophotometer and Qubit 2.0 flurometer (Thermo Scientific). 1µg genomic DNA was bisulfite-treated using the EZ DNA Methylation™ Kit (Zymo Research) following the manufacturer's recommended protocol.

A 341 bp fragment corresponding to our region of interest in the FKBP5 gene intron 7 was amplified by polymerase chain reaction (PCR) using 20 ng of bisulfite-converted DNA. The PCR reaction used 0.65 U EpiMark® Hot Start Taq DNA Polymerase (New England Biolabs® Ltd.) in the provided reaction buffer, 0.2 mM dNTPs and 0.2 µM of the following primers: FKBP5-in7_F: 5'-TGGGATAATAATTTGGAGT TATAGTGTAGG-3' and FKBP5-in7_R: /5Biosg/AAATTTATCTCTTA CCTCCAACACTAC-3' (IDT Inc.).

The PCR cycling conditions were as follows: 95°C for 1 min followed by 45 cycles of 95°C for 30 seconds, 59°C for 1 minute and 68°C for 1 minute with a final extension of 5 minutes at 68°C.

The PCR products were sequenced using the PyroMark Q96 platform (Qiagen) following the manufacturer's recommended protocol using the CFI Imaging and Molecular Biology Platform at McGill University in the Department of Pharmacology and Therapeutics.

The following sequencing primers were used: FKBP5_S3A: ATTTTT GTGAAGGGTATAATT and FKBP5-in7_S67: A5'-GTTGATATATAG GAATAAAATAAGA-3' (IDT Inc.) to assess CG-6 and CG-7 following the numbering of Resmini et al., 2015, which correspond to Bin3, CG1-2 called by Klengel et al., 2013. Percentage methylation levels and quality control were analyzed using PyroMark CpG Software 1.0.11 (Qiagen). The average methylation level of two independent runs were used at each CG-site in the analyses.

10

MAGNETIC RESONANCE IMAGING

Magnetic resonance images were obtained with a Philips Achieva 3 Tesla MRI scanner at both the CAMI (8 channel receiver coil) and TCIN (32 channels receiver coil) sites.

For detailed sequence parameters, see Appendix e for the CAMI dataset and Appendix f for the TCIN dataset.

10.1 ACQUISITION

10.1.1 *T1 MRI*

To assess volume and cortical thickness of brain regions in all our subjects, we collected a high-resolution 3D T1-weighted structural dataset.

For the CAMI dataset, sequence parameters were as follows: 160 axial high-resolution T1-weighted SPGR slices time of repetition (TR): 8.5 ms, time of echo (TE): 3.9 ms, in-plane resolution: $1 * 1$ mm^2, slice thickness: 1 mm, flip angle: 8°.

In the TCIN dataset, sequence parameters were as follows: 180 axial high-resolution T1-weighted SPGR slices TR: 8.4 ms, TE: 3.8 ms,in-plane resolution: $0.898 * 0.898$ mm^2, slice thickness: 0.9 mm, flip angle: 8°.

10.1.2 *Functional MRI*

After the structural scan, an fMRI task was run. For the CAMI dataset, acquisition parameters were as follows: spin echo type echo planar imaging (SE-EPI) sequence, 550 dynamic scans, TR: 2000 ms, TE: 35 ms, in-plane resolution: $3 * 3$ mm^2, slice thickness: 4.8 mm.

In the TCIN dataset, sequence parameters were as follows: SE-EPI sequence, 550 dynamic scans, TR: 2000 ms, TE: 25 ms, in-plane resolution: $3 * 3$ mm^2, slice thickness: 3 mm.

10.1.3 *Functional MRI task*

The same task was run at both sites. Its goal was to investigate the activity of brain regions involved in voluntary emotion regulation. Participants were asked to process visual stimuli projected on a screen behind them and viewed by a mirror placed in front of their eyes. The task was event-related and consisted of 180 pseudo-randomized trials. The trial order was the same of all subjects. Each trial consisted of a fixation cross of jittered duration (mean: 1.5 s, range: 1-1.8 s), followed by a viewing stage in which positive, negative or neutral rectangular pictures from the international affective pictures database (IAPS) were shown for 2 seconds. One and a half seconds after seeing the picture, participants were either asked to focus on the shape of the picture and answer whether this was horizontal or vertical or had to answer a question about its valence (positive, negative or neutral). Participants did not know beforehand which question would be asked and could not respond until the question was shown. From here on, we will label the first type of trial shape recognition trials (SRT) (Figure 6 A) and the second emotion recognition trials (ERT) (Figure 6 B). The same amount (30) of ERT and SRT was delivered for each of the three valences (positive, negative, neutral). Standardized training outside of the scanning preceded performing the task.

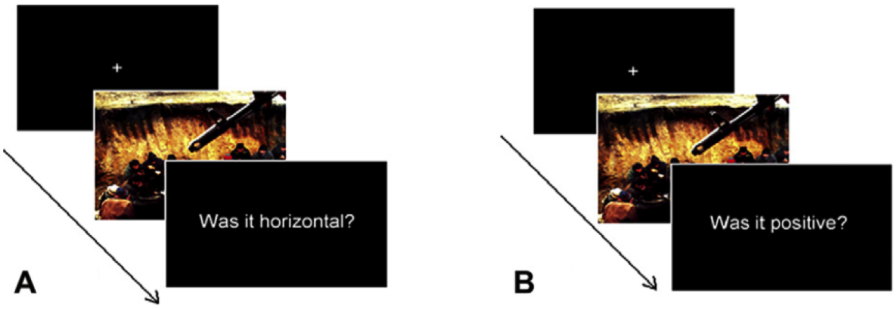

Figure 6 – Two types of trials used in the task. A. Shape recognition trial: a picture with negative emotional valence is followed by a question about its shape. B. Emotion recognition trial: a picture with negative emotional valence is followed by a question referring to said valence. Both pictures are preceded by a fixation cross. Adapted from Lisiecka et al., 2012.

10.1.4 *Behavioural task analysis*

In our studies, to parsimoniously assess valence, trial type and diagnosis effects across all our behavioural measures, which were repeated within-subject, we investigated these data using generalized estimated equations as implemented in SPSS 22 (IBM).

Thus, we entered in one comprehensive linear scale model the number of hits for each condition and the following independent variables: trial type and valence (within-subject factors), diagnosis, age and sex (between-subject factors). In studies investigating the rs1360780 SNP of FKBP5 (Chapters 12 and 13), we also added it as a between-subject factor (T* or CC).

Dependent variables were number of hits and reaction times, respectively. In each model we tested for the main effects of each variable and all interactions between diagnosis, valence and trial type.

If significant interactions were detected, each valence and trial type was then also explored individually.

10.1.5 *Diffusion magnetic resonance*

To assess integrity and shape of white matter fibers, a diffusion weighted scan was then performed with 61 diffusion directions at both sites.

For the CAMI dataset, acquisition parameters were as follows: sense encoding (SENSE) sequence with b-weight of 1200, 60 slices, TR: shortest ms, TE: 59 ms, in-plane resolution: $1.88 * 1.88$ mm^2, slice thickness: 2.10 mm.

In the TCIN dataset, sequence parameters were as follows: SENSE sequence with b-weight of 1500, 65 slices, TR: shortest, TE: shortest, in-plane resolution: $2 * 2$ mm^2, slice thickness:2 mm.

10.2 DATA PROCESSING

All analyses were conducted using MATLAB® (MathWorks), version R2014a (8.3.0.532) running on a iMac (21.5-inch, Late 2013). Computer specifications were: processor: 2.9 GHz Intel Core i5; memory: 8 GB 1600 MHz DDR3; graphics: NVIDIA GeForce GT 750M 1024 MB.

10.2.1 *Structural MRI*

Structural data was processed with statistical parametric mapping 12 (SPM12) (http://www.fil.ion.ucl.ac.uk/spm) and with the computational anatomy toolbox 12 (CAT12) , http://www.neuro.uni-jena.de/vbm/download/). CAT12 provides a set of functions that expand those of SPM12 to perform voxel-based morphometry (VBM) on structural MRI images, returning the voxel-wise estimation of the local amount or volume of grey matter (Ashburner and Friston, 2005).

The segmentation pipeline of CAT12 was run on all T1 images using default parameters to obtain Montreal neurological institute (MNI) normalized and modulated structural segmented data for all subjects. In detail, this procedure is based on an adaptive maximum a posteriori technique. In comparison with the unified segmentation approach suggested by Ashburner and Friston, 2005, CAT12 uses tissue probability maps only to spatially normalize the images to standard MNI space.

These maps are available within SPM12 and are provided by the International Consortium for Brain Mapping (http://www.loni.ucla.edu/ICBM/ICBM_TissueProb.html). They are derived from 452 T1-weighted scans, which were aligned with an atlas space and corrected for scan inhomogeneities. All voxels from these structural images were classified into grey matter, white matter, cerebro-spinal fluid, bone, non-brain soft tissue and air outside of the head and in nose, sinus and ears. These data were then affine registered to the MNI space and down-sampled to 2 mm resolution. Prior probability maps were finally generated by averaging tissue classes over subjects. The final images give the prior probability of any voxel in a registered image being of any of the tissue classes irrespective of its intensity.

The algorithm used by CAT12 employs these tissue probability maps for the initial spatial transformation to MNI space using a mutual information affine regularisation to estimate a nonlinear deformation field that best overlays the probability maps on the individual subjects' images (D'Agostino et al., 2004). Local variations of the parameters (i.e. means and variance) are also modelled as slowly varying spatial functions to account for inhomogeneities or other local variations of intensity (Rajapakse, Giedd, and Rapoport, 1997). This normalization is then perfected by the use of DARTEL (Ashburner, 2007), an algorithm for diffeomorphic image registration that uses a template

derived from 555 healthy control subjects of the IXI-database (http://www.brain-development.org).

After the initial segmentation into three pure tissue classes (GM, WM, CSF), CAT12 then uses a partial volume estimation with a simplified mixed model of two additional mixed classes: GM-WM and GM-CSF (Tohka, Zijdenbos, and Evans, 2004). This results in an estimation of the amount (or fraction) of each pure tissue type present in every voxel (as single voxels probably contain more than one tissue type) and thus provides a more accurate segmentation. Since spatial normalisation expands and contracts some brain regions, a modulation procedure is also performed to scale by the contraction, so that the total amount of grey matter in the final images remains the same as it would be in the original ones (see Figure 7 for an example of segmentation of one of our datasets).

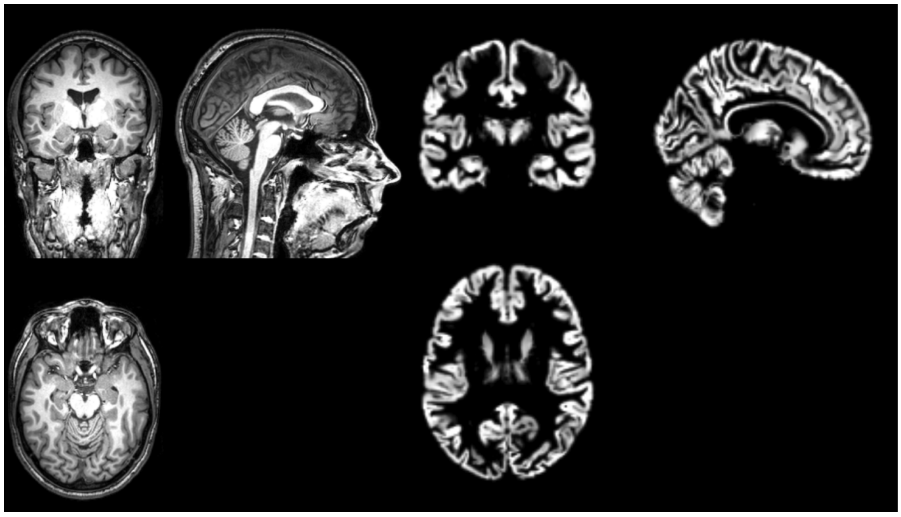

Figure 7 – Example of segmentation performed by CAT12. The original structural scan (left) was segmented and warped into standard Montreal Neurological Institute space, returning an image showing the amount of gray matter in each voxel (right).

Warping fields for the forward transformation to MNI space were saved to be applied to the functional data of each corresponding subject. We also estimated total intracranial volume (TIV) and saved it for each subject to be used as a covariate in subsequent VBM analyses.

Quality control was performed as provided in CAT12 by displaying a slice for all segmented images and checking data homogeneity. The latter is computed based on the correlation between all images and the mean across subjects for each image: the smaller this correlation, the more a subject deviates from the sample mean.

10.2.2 *Functional MRI*

Functional data was processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The first pre-processing step conducted was realignment of the scans to the time series mean image to correct for motion. The routine uses a least squares approach and a 6 parameter rigid body spatial transformation. As output, it returns the realigned images and a set of parameters showing the offset of each scan compared to the mean along 3 translation and 3 rotation axes.

After this step, movement parameters of subjects were inspected and participants were excluded when movement exceeded 3 mm or 3 °in any direction. For motion between 2 and 3 mm, subjects were excluded if they presented movement spikes rather than a slow drift pattern (Figure 8).

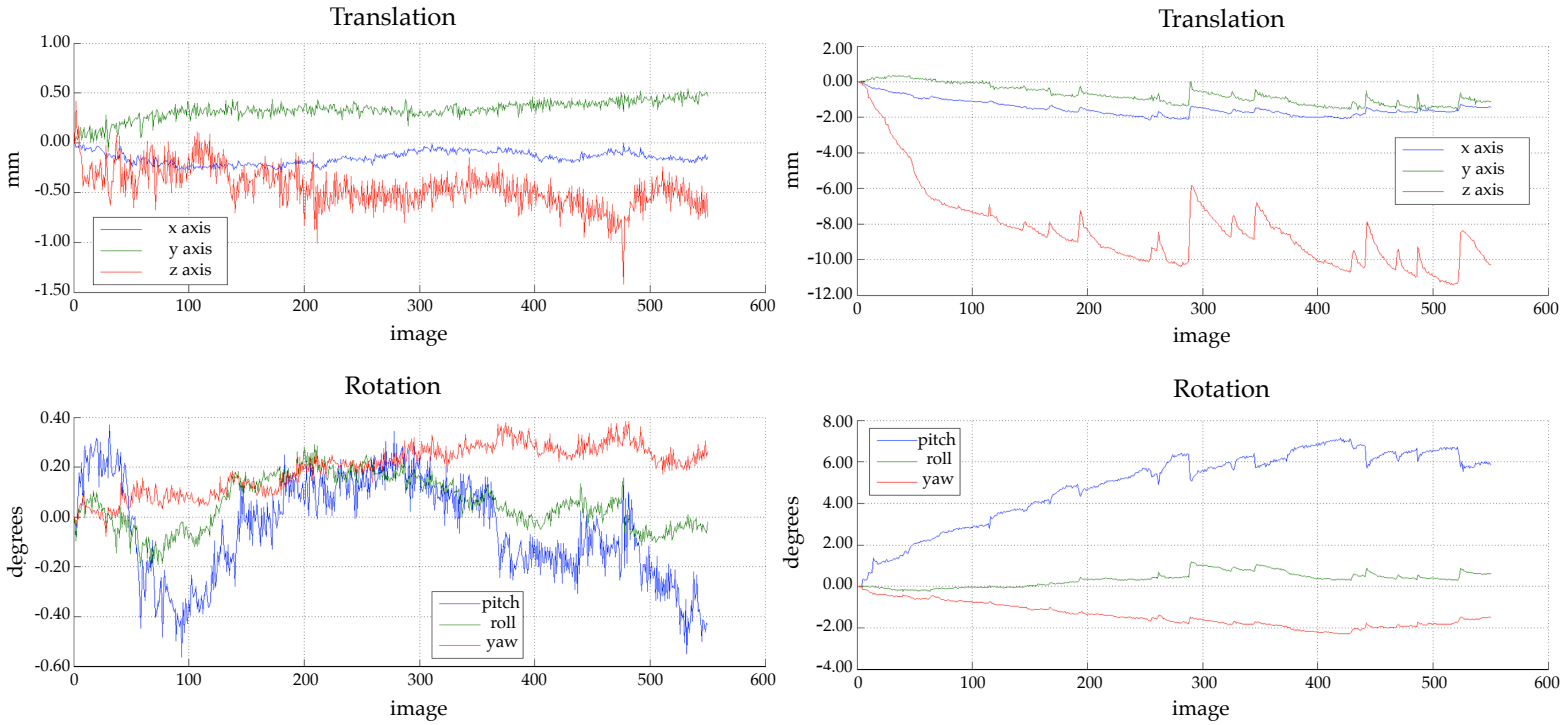

Figure 8 – Example of movement parameters as returned by SPM12 after realignment. The subject shown on the left side showed minimal motion along all directions during the 550 scans and was included in the functional analysis. The subject shown on the right side, on the other hand, was removed.

Then, differences in image acquisition time between slices were corrected so that each volume could be modelled as being acquired simultaneously. Since volumes are measured one slice at a time, without correction the data on one slice would represent a point in time removed from that of other slices. The slice timing routine in SPM12 "shifts" a signal in time to provide an output vector that represents the same signal sampled starting either later or earlier. This is accomplished by adding a constant to the phase of the sines that make up the signal after a Fourier transform, effectively realigning the data in time.

After this step, functional images were coregistered to their structural counterparts using an affine transformation similarly to what is described in Collignon et al., 1995. After this step, normalization to standard MNI space was conducted in SPM12 using the tissue probability maps provided in the toolbox in accordance to (Ashburner and Friston, 2005). For our study including a VBM analysis, it was possible to directly use the deformation fields computed for the transformation of the structural scans as described above to warp the functional data to standard MNI space.

Finally, whenever the functional data was used for whole-brain analysis, it was smoothed with a Gaussian kernel of width $8 * 8 * 8$ to suppress noise, improve the normality of its distribution and reduce effects due to residual differences in functional and gyral anatomy during inter-subject averaging.

For the statistical analysis of our fMRI data we used a mass univariate approach based on a general linear model (GLM). In SPM12, the procedure involves the specification of a GLM design matrix, filtering, estimation of GLM paramaters and finally interrogation of results using contrast vectors to produce statistical parametric maps.

Overall, the design matrix defines the experimental design and the nature of hypothesis testing to be implemented. It has one row for each scan and one column for each effect or explanatory variable (e.g. regressor or stimulus function). Expected responses are modelled by convolving the onset time and duration of a stimulus with a basis function that models the brain canonical haemodynamic response to it, such as the one depicted in Figure 2.

In SPM12, analysis of data from multiple subjects typically proceeds in two stages. The "first level" models are used to implement a within-subject analysis. To make inferences about the population from which the subjects were drawn, a mixed-effects analysis is then

implemented using the "summary-statistic" approach where contrast images from each subject are entered as data into a "second level" model.

After running our second level models, smoothness of the data was assessed by use of the SPM12 results window output, to assess compatibility with the assumptions of random field theory, which allow cluster-wise multiple comparisons correction as implemented by the software (Chumbley and Friston, 2009; Chumbley et al., 2010).

First and second level models used in our experiments will be presented in detail in each dedicated chapter.

10.2.3 *Psychophysiological interaction*

To analyse brain functional coupling between brain areas during our task conditions, we employed generalized psycho-physiological interaction (gPPI) as implemented by the gPPI toolbox (McLaren et al., 2012).

The term psycho-physiological interaction (PPI) refers to the idea of explaining responses in one cortical area in terms of an interaction between the influence of another region and some experimental task-related parameter (Friston et al., 1997). First of all, the mean time-series of the BOLD signal in a seed region is extracted. Then the onset times of the stimulus of interest are convolved with the canonical HRF as in the standard GLM procedure to obtain a representation of the expected brain responses to the event. Subsequently, a PPI regressor is generated as the element-by-element product of the HRF convolved task vector and seed region of interest (ROI) timeseries (Figure 9).

Once these regressors have been obtained, a GLM analysis is run in which the variable of interest is the interaction term. The seed time-series and the expected brain response to the stimulus are entered as covariates of no interest in this analysis, in order to isolate areas that show increased coupling only during the condition of interest compared to all other conditions.

Compared to standard PPI procedures, gPPI provides a way to automatically accommodate more than two task conditions in the same PPI model (McLaren et al., 2012).

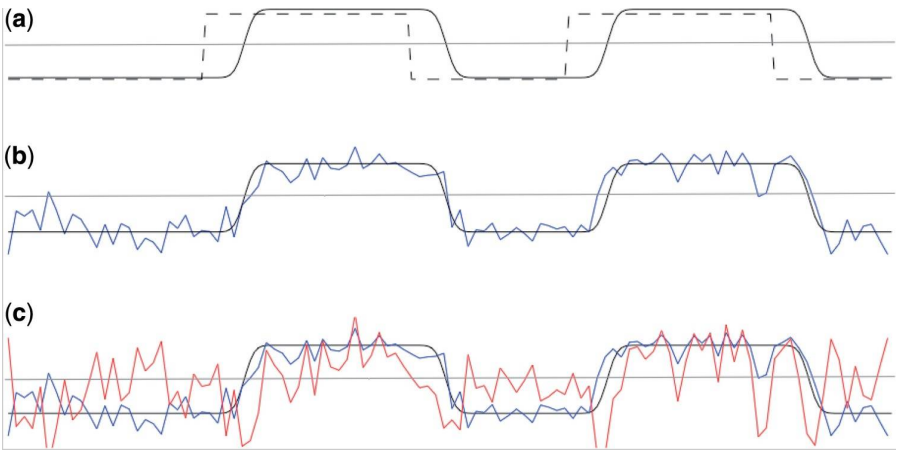

Figure 9 – To generate a PPI regressor, first (a) the stimulus exposure (dashed line) is convolved with a canonical hemodynamic response function (HRF, black line). Then, (b) a time course from a seed region of interest is extracted (blue line). If this region of interest is active during the task, this vector will be correlated with the HRF convolved task regressor. (c) The PPI regressor (red line) is the product of the HRF convolved task (black line) and seed ROI (blue line) regressors. Adapted from O'Reilly et al., 2012.

10.2.4 *Diffusion magnetic resonance*

Data were pre-processed and analysed using ExploreDTI (http://www.exploredti.com).

First of all, motion correction was applied to all data, aligning all diffusion-weighted volumes to the first non weighted one (Leemans and Jones, 2009). Two sources of noise in the image were then taken into account: eddy currents and echo planar imaging (EPI) distortions.

Eddy currents are circular electric phenomena induced within conductors by a changing magnetic field in the conductor, due to Faraday's law of induction. During the acquisition of diffusion images they might cause shear, false fiber tracking, enhanced background, image intensity loss, and image blurring. These distortions depend on the orientation of the gradients used, this is why ExploreDTI takes this information into account to correct the images for eddy current-induced image distortion (Leemans and Jones, 2009; Rohde et al., 2004).

EPI distortion is caused by inhomogeneities in the applied magnetic field. An inhomogeneous magnetic field results in geometric distortion and loss of signal in the diffusion images. ExploreDTI is able to use the structural T1 image of each subject to unwarp the diffusion data, thus correcting for this effect (Irfanoglu et al., 2012).

After pre-processing, we reviewed the diffusion tensor imaging (DTI) data by visually inspecting the slice images ensuring that trans-

lational head movement during scanning was less than 3 mm in all directions.

Diffusion tensor estimation was conducted with a robust non-linear approach: REKINDLE, that takes into account the influence of outliers on the tensor model estimates (Tax et al., 2015). Then, we used the "extract diffusion measures from atlas labels" tool in ExploreDTI, which performs a non-linear registration of each subject's image into standard space and defines regions for it based on the automatic anatomical labeling (AAL) atlas (http://qnl.bu.edu/obart/explore/AAL/). These are then warped back into subject space and used for the extraction of diffusion measures from the original images for each subject.

All figures were drawn using BrainNet viewer (Xia, Wang, and He, 2013).

Part III

STUDIES

11

FMRI OF EMOTION RECOGNITION AND REGULATION

11.1 BACKGROUND

As previously briefly mentioned in Chapter 4, over the past decade several hypotheses have emerged concerning how cognitive processing of emotion takes place (see Ochsner and Gross, 2005; Ochsner, Silvers, and Buhle, 2012; Dolcos, Iordan, and Dolcos, 2011; Rive et al., 2013 for reviews). In particular, Phillips et al. have identified two groups of regions that are thought to play a major role in this process and labelled them the ventral and dorsal systems (Phillips et al., 2003a).

The ventral system comprises the amygdala, insula, ventral striatum, ventral ACC, as well as the VMPFC and OFC. The dorsal system, on the other hand, includes the hippocampus, dorsal anterior cingulate cortex (dACC), dorsomedial prefrontal cortex (DMPFC) and dorsolateral prefrontal cortex (DLPFC). The ventral system appears to be involved in identifying emotionally salient stimuli and generating an appropriate affective state, whereas the dorsal system plays a role in the voluntary top-down regulation of emotional responses (Ochsner and Gross, 2005; Phillips et al., 2003b; Phillips et al., 2003a).

In an attempt to model how regulation of emotion takes place, a fundamental distinction has been made between voluntary and automatic (or implicit) processes (Rive et al., 2013). Automatic processing is thought to involve predominantly the medial prefrontal cortical structures, such as the dACC, sgACC), OFC, DMPFC and VMPFC, but also the hippocampus and parahippocampal gyri (Hamilton et al., 2012; Phillips, Ladouceur, and Drevets, 2008). Voluntary processes, on the other hand, appear to recruit lateral prefrontal cortical regions (Rive et al., 2013).

Beside the distinction between automatic processing and voluntary regulation, it is also necessary to take into account the strategy that is employed. Overall, three main mechanisms can be identified and each involves automatic and voluntary processing: behavioural, cognitive and attentional control. Behavioural control involves alter-

ing a response to emotion or its expression. Cognitive control alters the emotional meaning of salient stimuli through mechanisms such as reappraisal and expectancy, whereas attentional control refers to the engagement or disengagement of attention to emotional stimuli (Phillips, Ladouceur, and Drevets, 2008).

MDD features both incongruent generation and interpretation of emotion (Bylsma, Morris, and Rottenberg, 2008) and an impaired ability to engage effective regulation of emotional responses (Rive et al., 2013; Gotlib and Joormann, 2010). This is why many paradigms have been used to assess differences in the brain regions recruited by all these processes between HC and MDD patients (see Rive et al., 2013 for a review). In particular, MDD often features an attentional deficit and biased allocation to negative stimuli (Murrough et al., 2011). Consequently, many studies have been conducted specifically investigating attentional control, analysing the neural correlates of both its automatic and voluntary modalities.

During automatic processing, findings have indicated increased activity in MDD patients in medial prefrontal regions (DMPFC and ACC). This was found mostly in tasks involving the regulation of negative emotions compared to other valences (Eugène et al., 2010; Etkin, Egner, and Kalisch, 2011; Canli et al., 2004). Moreover, increased connectivity between some of these regions and the amygdala were detected in patients with MDD compared to controls (Almeida et al., 2011). Studies also reported that patients show a compensatory recruitment of parietal and lateral prefrontal regions while redirecting attention away from interfering emotions (Bertocci et al., 2012; Frodl et al., 2009), although overall findings remain mixed and potentially biased by treatment effects (Chen et al., 2007; Fales et al., 2009; Rive et al., 2013).

Concerning voluntary attentional control, studies have shown increased venterolateral prefrontal cortex (VLPFC) activity in patients (Dichter, Felder, and Smoski, 2009; Elliott et al., 2002; Wang et al., 2008) and stronger effective connectivity between medial structures (such as the sgACC) and the amygdala (Carballedo et al., 2011; Almeida et al., 2011), although Matthews et al., 2008 report decreased connectivity between these structures correlated with depression severity. Findings regarding the involvement of DLPFC have once again been mixed, showing increased (Dichter, Felder, and Smoski, 2009; Fales et al., 2009; Townsend and Altshuler, 2012), decreased (Wang et al., 2008) or similar activity compared to controls (Townsend et al., 2010).

Overall, the most effective paradigms in highlighting differences in attentional control of emotion between HC and MDD so far have been the ones involving automatic processing. Findings in voluntary paradigms are not unequivocally conclusive, possibly due to reduced sample sizes, clinically heterogeneous samples and differences in task designs (Rive et al., 2013).

So far, few studies have assessed the influence of brain areas directly activated by emotional regulation and recognition on other regions in a network-based approach. Indeed, recent findings suggest that cognitive control of emotion is modulated by a dynamic interplay of systems that may often overlap and influence each other and that to advance our understanding of psychiatric disorders more knowledge is needed about the functional networks involved (Okon-Singer et al., 2015). Overall, during emotional tasks, MDD patients have been reported to show connectivity alterations between regions involved in emotional responses, such as the sgACC (Hall et al., 2014) and the insula (Henje et al., 2015) with a wide array of brain areas, including ones belonging to the ventral and dorsal emotional regulation complexes, but also to the default mode network and visual system. These findings suggest that emotional processing alterations in these patients might involve a complex interplay between different functional networks.

Our goal was to investigate the functional behaviour in brain networks recruited during emotion recognition and regulation in MDD patients and healthy controls. To do this, we employed the task used in previous work from our group (Lisiecka et al., 2012), which required participants to either evaluate the valence of salient stimuli or to shift their attention away from them by assessing their shape (voluntary attentional regulation of emotion). We identified which regions were recruited in each of the trial types and which other regions were influenced by their activity using a gPPI approach (see Chapter 10 for a detailed description). Finally, we investigated if the responses and networks recruited were different between controls and MDD patients.

We hypothesised an increased recruitment of dorsal and lateral prefrontal cortical regions across subjects during the trials involving voluntary attentional shift and a primary involvement of medial prefrontal regions in valence recognition ones, as an expression of unhindered emotion generation and interpretation. Also, we expected

functional connectivity changes of these regions with areas involved in the generation of affect such as the amygdala and ventral striatum.

We thought that patients, if exposed to emotional stimuli, would show altered responses in medial prefrontal regions, amygdala, insula and DLPFC. Finally, we believed these regions would also show abnormalities in functional connectivity in patients compared to controls.

11.2 MATERIALS AND METHODS

11.2.1 *Sample*

The study was run on a subset of the TCIN dataset (see Chapter 7). It included 42 adult patients with MDD and 37 HC subjects (Table 4).

11.2.2 *Rating Instruments*

Self and observer rated scales were also filled out for all participants (see Chapter 8 for details).

As measures of clinical severity, the HAMD (Hamilton, 1986) and BDI (Beck et al., 1961) were used.

11.2.3 *fMRI analysis*

See Chapter 10 for details on the fMRI sequence and task employed.

11.2.3.1 *Preprocessing*

Data was analysed with SPM12 and preprocessed as described in Chapter 10.

After the motion correction step, 8 patients and 2 controls were excluded. Then co-registration of each participant's structural image to the mean of the motion corrected functional images, slice time correction, spatial normalization and smoothing using an 8 mm full-width at half maximum (FWHM) Gaussian kernel were applied.

11.2.3.2 *First level analysis*

The regressors entered in the first-level GLM analyses were the 6 time vectors of the questions' onsets and the 6 motion regressors. Then, t-test contrasts were calculated as follows:

1. SRT versus ERT
2. Negative trials versus neutral
3. Positive trials versus neutral
4. Interaction between trial type and valence (2 contrasts)

11.2.3.3 *Second level analysis*

Age and sex were used as covariates for all second level tests.

To assess the main effect of SRT versus ERT regardless of diagnosis, we ran a one-sample t-test of the SRT versus ERT contrasts (1) of all subjects from the first level analysis. To test for an interaction effect between group and trial type, we used the same contrast (1), but ran a 2 independent samples t-test instead, comparing patients and controls.

To assess the effect of valence, we ran a factorial model with 2 non-independent levels. Each of the valence effects contrast maps (2, 3) was entered into the model. We proceeded in the same way to test for effects of the interaction between valence and trial type across subjects, using contrast maps (4).

Then, to test for an interaction valence and group, we entered the first level valence contrasts (2,3) in a factorial model with one factor with 2 independent levels (group) and one factor with two non-independent levels (valence). We finally proceeded in the same way using the interaction contrasts (4) to test for a triple interaction between type, valence and group.

Interaction effects were tested at the second level using F tests followed by post-hoc t-tests on the mean beta values extracted from the cluster. To determine the significance of results, a threshold of $p<0.05$ family wise error (FWE) at cluster level following $p<0.005$ whole-brain voxel level was used.

11.2.3.4 *Psycho-physiological interaction*

First of all, we identified the regions that were more active during SRT compared to ERT and, conversely, those that were more active during ERT compared to SRT across all subjects. Due to the large dimension of the resulting clusters, activation maps were first thresholded at $p<0.05$ FWE whole-brain voxel level, then the AAL atlas was used (ht tp://qnl.bu.edu/obart/explore/AAL/) as a reference to differentiate the regions involved. For each region, we extracted the coordinates of the local activation peak.

We then built regions of interest as spheres of 6 mm radius centred on those coordinates using the MarsBar toolbox (Brett and Anton, 2002). We used each of these regions of interest as a seed region for our gPPI analysis.

gPPI analyses were conducted using the gPPI toolbox (McLaren et al., 2012) to generate first level models including a gPPI term for each of our experimental conditions for each of our seed ROI. This approach has been shown to have a greater sensitivity and specificity compared to the standard PPI implementation in SPM12, especially in tasks involving more than two conditions (see Chapter 10 for details).

Using the gPPI conditions, we conducted the same first and second level analyses as previously described for task responses, therefore assessing the main effects and interactions of group, trial type and valence on the functional coupling of each ROI with the rest of the brain. Age and sex were used as covariates for all second level models. Interaction effects were tested at the second level using F tests.

To determine the significance of findings, a threshold of $p<0.05$ FWE at cluster level following $p<0.005$ whole-brain voxel level (minimum cluster size = 0) was used. Then, to account for multiple seed ROI testing, we considered significant only those results that had a p value less than $0.05/27=0.00185$. The size of the smallest significant cluster was then used as a threshold to present only significant results in figures and tables.

After identifying regions that showed task and gPPI effects involving the group factor, we extracted the mean beta values of all conditions in these clusters from our first level models and entered them in statistical package for the social sciences (SPSS) 12 (IBM) for statistical analysis (when the difference was present across multiple conditions, betas were averaged to match the second level contrasts). Post-hoc t-tests were conducted on these values testing for the effect of group for each condition in a linear regression including age and sex as confounds. To account for multiple comparisons, false detection rate (FDR) correction was used.

11.2.4 *Behavioural analysis*

Hits and reaction times in the task were analysed as described in detail in Chapter 10.

Furthermore, to investigate whether the functional differences relate to task performance, we calculated Spearman correlations be-

tween the mean beta values (adjusted for age and sex) in the conditions showing an effect of group and the number of hits in the corresponding trial type within the patient group.

11.2.5 *Effect of medication*

Within the patient group, we finally similarly performed t-test analyses (medicated versus unmedicated) to investigate the effect of medication on our significant findings.

11.3 RESULTS

11.3.1 *Demographics*

For demographics of the final sample see Table 4.

	HC	MDD	Test (p)
N	35	34	
Age (years)	30.06 ± 9.25	33.35 ± 9.83	t=-1.434 (0.16)
Sex (F/M)	23/12	22/12	χ^2=0.93 (1.00)
HAMD	0 (0-8)	22 (6-33)	U=1,188.500 (<0.01)
BDI	1 (0-13)	34 (17-50)	U=383.500 (0.01)
CTQ	27 (25-53)	41 (25-88)	U=585.500 (<0.01)
Medication		9/15/9/1	
Illness duration (years)		2.98 (0-21)	

Table 4 – Demographic and questionnaire scores. For parametric variables, mean and standard deviation are given. For non-parametric variables, the median as well as minimum and maximum values are given. Medication is expressed as none/SSRI/SNRI/other (antipsychotic or agomelatine). HC=healthy controls; MDD=depressed patients; HAMD=Hamilton depression scale; BDI=Beck depression inventory; CTQ=childhood trauma questionnaire; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors.

11.3.2 *Behavioural analysis*

Concerning the number of hits, MDD performed worse across all trials (Wald χ^2=7.13, p<0.01) and we detected an interaction between diagnosis, trial type and valence (Wald χ^2=41.69, p<0.01). Analysis of individual trials revealed that patients showed less hits especially in negative and positive ERT, as well as neutral and negative SRT (see Table 5).

For response times, a triple interaction between diagnosis, trial type and valence was observed (Wald χ^2=41.22, p<0.01), but examination of the individual trials showed no effect of diagnosis. This result was probably driven by faster responses during negative and positive trials compared to neutral across all trial types (t=4.93, p<0.01).

	HC	MDD	Wald χ^2 (p)
Hits ERT Neu	22.97 ± 4.47	23.32 ± 4.24	1.20 (0.27)
Hits ERT Neg	26.00 ± 3.91	23.26 ± 7.46	7.26 (<0.01)
Hits ERT Pos	22.67 ± 5.05	20.29 ± 6.90	5.53 (0.02)
Hits SRT Neu	25.27 ± 4.87	21.90 ± 8.32	5.80 (0.02)
Hits SRT Neg	24.36 ± 4.65	21.23 ± 7.56	5.44 (0.02)
Hits SRT Pos	24.09 ± 4.65	21.84 ± 6.93	3.34 (0.07)
RT ERT Neu (s)	1.22 ± 0.31	1.23 ± 0.26	0.43 (0.51)
RT ERT Neg (s)	1.07 ± 0.30	1.07 ± 0.24	0.46 (0.49)
RT ERT Pos (s)	1.15 ± 0.27	1.18 ± 0.28	0.04 (0.85)
RT SRT Neu (s)	1.24 ± 0.32	1.25 ± 0.31	0.15 (0.69)
RT SRT Neg (s)	1.08 ± 0.30	1.07 ± 0.24	0.46 (0.49)
RT SRT Pos (s)	1.25 ± 0.23	1.30 ± 0.33	0.13 (0.72)

Table 5 – Task performance. Hits, misses and incorrect responses are given as counts, RT are given as seconds. Tests show the results for our generalized estimation equations analysis. Overall effect of diagnosis on hits was significant across all trials (Wald χ^2=7.13, p<0.01). HC=healthy controls, MDD=depressed patients, RT=reaction time, SRT=shape recognition trials, ERT=emotional recognition trials, Neu=neutral, Neg=negative, Pos=positive.

11.3.3 *fMRI activation analysis*

All responses to task effects are presented in detail in Table 6 and Figure 10.

11.3.3.1 *Effect of trial type*

SRT compared to ERT showed a significantly increased response in the bilateral supramarginal gyri, superior parietal lobuli, superior occipital gyri, middle frontal gyri, inferior temporal gyri, precentral gyri as well as in the left fusiform gyrus and left exterior cerebellum.

ERT compared to SRT presented a significant increase in hemodynamic activity bilaterally along the entirety of the medial frontal cortex, including both the pregenual and subgenual subdivisions of the ACC. Furthermore, activation was detected in the bilateral temporal pole, middle temporal lobes, amygdalae, left anterior insula, posterior

cingulate cortex, angular gyri, triangular part of the inferior frontal gyri, left lateral orbital gyrus, fusiform gyri and a cluster in the left exterior cerebellum.

11.3.3.2 *Effect of valence*

The middle temporal, occipital, fusiform and lingual gyri, precuneus as well as the medial and superior frontal lobe showed an effect of valence, with positive and negative trials eliciting greater responses compared to neutral.

11.3.3.3 *Interaction between trial type and valence*

The occipital and fusiform gyri as well as the anterior cingulate gyrus showed an interaction between the trial type and valence factors.

Contrast	Cluster p_{FWE}	Voxels	Value	Peak	Region
SRT>ERT	<0.001	6949	14.18	42 -43 47	R supramarginal gyrus
			12.96	-12 -70 47	L superior parietal lobule
			12.91	27 -64 53	R superior parietal lobule
	<0.001	1470	9.99	27 8 53	R middle frontal gyrus
			9.31	27 8 53	R middle frontal gyrus
			7.17	48 35 29	R precentral gyrus
	0.014	272	8.73	51 8 20	L middle frontal gyrus
			4.68	-45 35 26	L middle frontal gyrus
			4.30	-36 44 11	L middle frontal gyrus
	0.008	303	7.56	-48 5 26	L precentral gyrus
			5.20	-57 11 32	L precentral gyrus
			3.56	-60 8 17	L precentral gyrus
	0.026	235	6.71	-27 -61 -31	L cerebellum
			5.72	-42 -43 -40	L cerebellum
			5.13	-30 -40 -43	L cerebellum
	0.038	215	4.32	24 -55 -13	R fusiform gyrus
			4.11	39 -40 -37	R fusiform gyrus
ERT>SRT	<0.001	9759	15.15	-6 53 35	L superior frontal gyrus

Contrast	Cluster p_{FWE}	Voxels	Value	Peak	Region
			14.67	-3 53 -7	L medial frontal cortex
			14.61	-12 41 44	L superior frontal gyrus
	0.005	335	12.72	33 -79-34	R cerebellum
			12.59	18 -85 -37	R cerebellum
			5.18	48 -61 -40	R cerebellum
Effect of valence	<0.001	13807	151.82	51 -73 2	R inferior orbital gyrus
			114.62	9 -79 -7	R lingual gyrus
			112.22	6 -88 2	R calcarine gyrus
	<0.001	2205	67.46	0 38 -19	R middle frontal gyrus
			57.02	-6 62 23	R superior frontal gyrus
			55.59	-3 56 11	L superior frontal gyrus
	0.024	177	13.79	-12 2 44	L middle cingulate cortex
			12.67	-24 -10 53	L superior frontal gyrus
			8.68	-32 2 53	L superior frontal gyrus
	0.034	164	9.09	42 44 14	R middle frontal gyrus
			8.16	36 47 -4	R medial frontal cortex
Valence*type	<0.001	7885	59.14	48 -73 2	R inferior orbital gyrus
			45.00	-45 -79 5	L inferior orbital gyrus

Contrast	Cluster p_{FWE}	Voxels	Value	Peak	Region
			42.02	42 -79 -4	R inferior orbital gyrus
	<0.001	984	27.89	-3 35 -1	L anterior cingulate cortex
			14.68	9 41 -7	R superior frontal gyrus
			14.00	12 11 -4	R caudate
	<0.001	329	19.62	48 32 20	R middle frontal gyrus
	0.023	160	10.20	-42 29 20	L middle frontal gyrus
			8.96	-48 29 26	L middle frontal gyrus
			8.15	-42 11 26	L inferior frontal gyrus

Table 6 – fMRI activation results not involving the group factor. $p_{FWE}<0.05$ at cluster level following $p<0.005$ whole-brain voxel level (minimum cluster size=0). HC=healthy controls; MDD=depressed patients; SRT=shape recognition trials; ERT=emotional recognition trials; L=left, R=right.

11.3.4 *Psychophysiological interaction*

We identified 10 local maxima for SRT versus ERT and 17 for ERT versus SRT, each of them belonging to a different region as defined by the AAL atlas (Figure 10). For their coordinates, see Table 7.

gPPI effects not involving the group factor are presented in detail in Table 8.

Trial	Region	Name	Centre	Label
SRT	R superior occipital gyrus	R SOG	21 -67 38	1
	L superior occipital gyrus	L SOG	-27 -64 38	2
	R middle frontal gyrus	R MFG	45 38 26	3
	L middle frontal gyrus	L MFG	-48 35 29	4
	R inferior temporal gyrus	R ITG	51 -61 -10	5
	L inferior temporal gyrus	L ITG	-54 -52 -13	6
	R precentral gyrus	R PCG	45 2 26	7
	L precentral gyrus	L PCG	-48 8 29	8
	R superior parietal lobule	R SPL	27 -64 53	9
	L superior parietal lobule	L SPL	-15 -70 47	10
ERT	middle cingulate	MFC	-6 53 35	11
	R temporal pole	R TP	45 20 -34	12
	L temporal pole	L TP	-39 20 -31	13
	R middle temporal gyrus	R MTG	63 -1 -19	14
	L middle temporal gyrus	L MTG	-60 -13 -13	15
	R amygdala	R AMY	21 -7 -13	16
	L amygdala	L AMY	-21 -7 -19	17
	posterior cingulate	PCC	-3 -49 29	18
	R angular gyrus	R AG	54 -61 29	19
	L angular gyrus	L AG	-48 -64 26	20
	R inferior frontal gyrus	R IFG	57 29 -1	21
	L inferior frontal gyrus	L IFG	-48 29 -1	22
	L lateral orbital lobe	L LO	-36 41 -10	23
	R fusiform gyrus	R FUS	39 -46 -19	24
	L fusiform gyrus	L FUS	-42 -46 -22	25
	pregenual anterior cingulate	pgACC	3 50 23	26
	subgenual anterior cingulate	sgACC	-6 47 -4	27

Table 7 – ROIs used as seed regions for the PPI analysis. ROIs were defined as 6 mm radius spheres centred on the peak values of the SRT>ERT and ERT>SRT contrast across all subjects. The AAL atlas was used as a reference to extract one peak from each of the regions involved. Abbreviations used throughout the text are shown and labels used in Figure 10. SRT=shape recognition trials, ERT=emotional recognition trials, L=left, R=right.

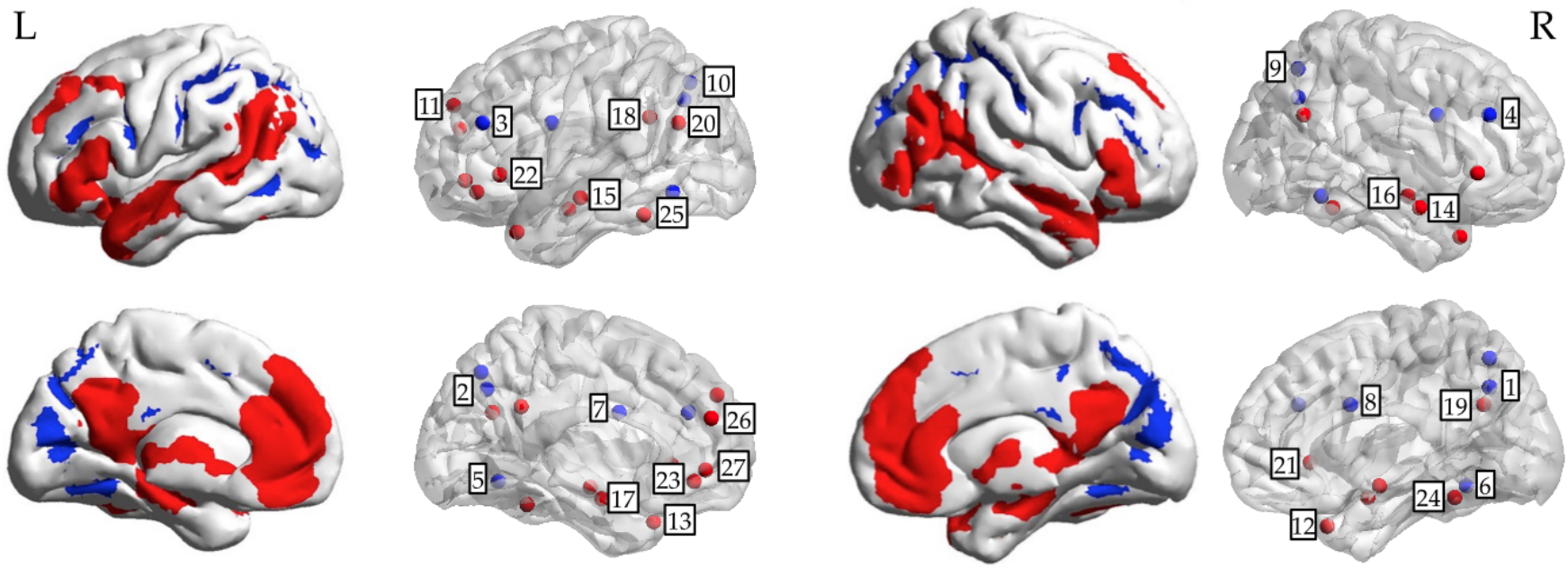

Figure 10 – Areas responding to SRT and ERT and gPPI ROIs. We show in lateral and medial views the result of our second level contrast across all subjects for ERT>SRT (red) and SRT>ERT (blue), p_{FWE}<0.05 at the cluster level following p<0.005 whole-brain voxel level. ROIs were defined as 6 mm radius spheres centred on the peak voxels in each of the resulting regions as defined by the AAL atlas. See Table 7 for ROI coordinates and labels. L=left hemisphere; R=right hemisphere; ERT=emotion recognition trials; SRT=shape recognition trials.

11.3.4.1 *PPI: Effect of trial type*

During ERT compared to SRT, the bilateral inferior temporal gyri, middle frontal cortex, right superior parietal lobule and precentral gyrus showed increased coupling with temporal areas and lateral frontal regions, such as the middle and inferior frontal gyri.

The right and left superior occipital gyri, the left superior parietal lobule and left inferior temporal gyrus, on the other hand, increased their functional connectivity with the middle and anterior cingulate cortex, precuneus and temporal gyrus.

Finally, the left temporal pole and right precentral gyrus showed increased coupling with the posterior cingulate gyrus, which in turn presented greater connectivity with the bilateral superior parietal lobuli.

11.3.4.2 *PPI: Effect of valence*

Functional coupling between the left fusiform gyrus and the posterior cingulate as well as between then middle frontal cortex and the precentral gyrus showed an effect of valence.

11.3.4.3 *Interaction between trial type and valence*

Coupling between the right inferior temporal gyrus and the left inferior frontal gyrus showed an effect of interaction between trial type and valence.

Contrast	Seed	Cluster p_{FWE}	Voxels	Value	Peak	Region
ERT>SRT	L ITG	<0.001	1919	6.00	48 -55 20	R angular gyrus
				4.60	42 -58 29	R angular gyrus
				4.51	48 -61 35	R angular gyrus
		<0.001	895	4.42	-51 -4 -16	L superior temporal gyrus
				4.41	-63 -34 8	L superior temporal gyrus
				4.06	-39 -1 -13	L insula
		<0.001	1103	4.33	-33 29 41	L middle frontal gyrus
				4.31	-6 23 26	L anterior cingulate cortex
				3.95	-9 50 5	L superior frontal gyrus
	L SOG	<0.001	1930	6.58	12 -61 32	R precuneus
				5.91	-6 -16 29	L middle cingulate cortex
				5.84	0 -25 41	L middle cingulate cortex
		<0.001	599	4.98	54 -43 29	R supramarginal gyrus
				4.30	51 -52 11	R middle temporal gyrus
				4.24	48 -49 53	R angular gyrus
	L SPL	<0.001	440	5.14	-6 -13 29	L middle cingulate cortex
				4.57	3 -25 41	R middle cingulate cortex
	L TP	<0.001	688	4.47	-15 -49 2	L precentral gyrus

Contrast	Seed	Cluster p_{FWE}	Voxels	Value	Peak	Region
				4.12	-12 -91 17	L superior occipital gyrus
				3.60	-6 -91 11	L cuneus
	MCC	0.001	393	4.38	-48 41 5	L inferior frontal gyrus
				4.37	-48 38 14	L inferior frontal gyrus
				4.28	-36 5 29	L precentral gyrus
	PCC	<0.001	1109	5.97	-27 -43 41	L superior parietal gyrus
				4.80	-24 -67 32	L superior parietal gyrus
		<0.001	980	5.97	33 -49 50	R superior parietal gyrus
				5.55	33 -49 41	R superior parietal gyrus
	R ITG	<0.001	2610	4.98	51 -52 14	R middle temporal gyrus
				4.95	60 -52 11	R middle temporal gyrus
				4.72	51 -46 32	R angular gyrus
			789	4.78	-60 -37 32	L supramarginal gyrus
				4.70	-54 -58 5	L middle temporal gyrus
				4.54	-54 -49 29	L supramarginal gyrus
			3617	4.61	-15 -25 38	L precentral gyrus
				4.60	-39 38 32	L middle frontal gyrus
				4.57	-6 -58 50	L precuneus

Contrast	Seed	Cluster p_{FWE}	Voxels	Value	Peak	Region
	R PCG	<0.001	2453	6.13	12 -43 32	R posterior cingulate cortex
				4.93	45 -43 2	R middle temporal gyrus
				4.90	39 -40 8	R middle temporal gyrusTG
		<0.001	1357	5.13	24 32 50	R superior frontal gyrus
				4.84	27 20 26	R middle frontal gyrus
				4.69	27 11 29	R middle frontal gyrus
	R SOG	<0.001	4016	6.30	51 -43 32	R supramarginal gyrus
				6.27	-3 -25 41	L middle cingulate cortex
				5.71	3 -52 44	R precuneus
		<0.001	3489	6.13	9 -58 47	R precuneus
				5.58	0 -25 41	L middle cingulate cortex
				5.56	6 -40 38	R posterior cingulate gyrus
	R SPL	<0.001	1022	5.87	48 -46 35	R angular gyrus
				5.10	51 -52 14	R angular gyrus
				4.75	48 -43 17	R superior temporal gyrus
Effect of valence	L FUS	<0.001	833	10.55	-18 -58 20	L precuneus
				10.53	-12 -52 5	L precuneus
	MCC	<0.001	657	15.57	27 -22 44	precentral gyrus

Contrast	Seed	Cluster p_{FWE}	Voxels	Value	Peak	Region
				11.84	24 14 26	precentral gyrus
				11.11	21 20 17	precentral gyrus
Trial type*valence interaction	R ITG	<0.001	250	4.06	-51 23 2	L inferior frontal gyrus
				3.87	-45 41 -13	L inferior frontal gyrus
				3.65	-39 23 -4	L inferior frontal gyrus

Table 8 – PPI results not involving the group factor. p_{FWE}<0.05 at cluster level following p<0.005 whole-brain voxel level, family wise error corrected for multiple ROI comparisons to p=0.00185. See Table 7 for seed abbreviations. HC=healthy controls; MDD=depressed patients; L=left; R=right.

11.3.4.4 *Interaction between trial type and diagnosis*

Controls compared to patients showed a greater differential response in ERT compared to SRT in the anterior insula. In particular, post-hoc testing revealed an increased response in controls in SRT compared to ERT (post-hoc test: t=-5.46, p_{FDR}<0.01) whereas in the MDD group no difference was found (post-hoc test: t=1.77, p_{FDR}=0.09) (Figure 11).

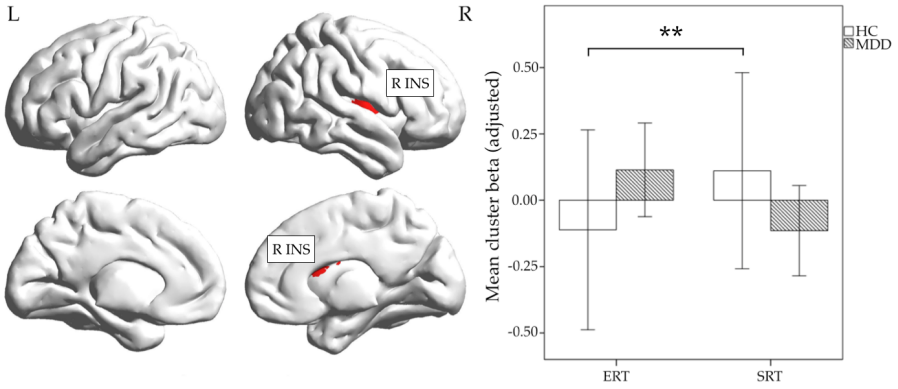

Figure 11 – Activation results showing the main effect of interaction during ERT>SRT for MDD>Controls. Lateral and medial views display the result of our second level gPPI analysis of the interaction effect (p<0.05 FWE at the cluster level following p<0.005 whole-brain voxel level). Bars show cluster mean beta values across all trials in each group adjusted for age and sex following linear regression (residuals). For post-hoc t-tests: p_{FDR}<0.05(*) and <0.01(**). Error bars are 95% confidence intervals. ERT=emotional recognition trials; SRT=shape recognition trials; MDD=major depression group; L=left; R=right; INS=insula.

11.3.4.5 *Effects of diagnosis on gPPI*

We report our gPPI results of between group comparisons in Table 9 as well as Figures 12, 13, 14.

Contrast	PPI Seed	Cluster p_{FWE}	Voxels	Value (t or F)	Peak	Region
MDD>HC	L FUS	0.001	555	4.18	51 44 -7	R inferior frontal gyrus
				4.15	42 -13 5	R insula
				4.05	42 -4 -1	R insula
	R IFG	<0.001	771	4.60	51 44 -4	R inferior frontal gyrus
				5.54	42 26 29	R middle frontal gyrus
				4.03	42 56 2	R middle frontal gyrus
Trial type*group	L IFG	0.001	291	18.23	-18 -13 26	L caudate
	R ITG	<0.001	331	18.48	39 -22 38	R precentral gyrus
					18 -13 41	R middle cingulate gyrus
					30 -31 41	R posterior cingulate gyrus
Valence*group	L AMY	<0.001	340	10.69	24 -76 -10	R fusiform gyrus
				10.40	-15 -55 -10	L lingual lobe
				9.62	21 -67 -13	R lingual lobe
Trial type*valence*group	L PCC	0.001	262	11.77	-3 -64 -1	L lingual lobe
				10.42	0 -46 5	posterior cingulate cortex
				9.69	18 -70 -10	R lingual gyrus
	R ITG	0.001	260	11.53	-51 23 2	L inferior frontal gyrus
				10.32	-45 41 -13	L inferior frontal gyrus
				9.42	-33 41 2	L middle frontal gyrus
	sgACC	0.001	236	11.00	-18 44 29	L superior frontal gyrus
				9.07	-21 50 20	L superior frontal gyrus
				8.76	0 41 26	L superior frontal gyrus

Table 9 – Between group gPPI fMRI results. Clusters are corrected for multiple ROI to p=0.00185 following p<0.005 whole-brain. See Table 7 for seed abbreviations. HC=healthy controls; MDD=depressed patients; L=left; R=right.

11.3.4.6 *Main effect of gPPI between groups*

Across all trials, MDD patients showed increased functional connectivity between the fusiform gyrus and the right inferior frontal gyrus (IFG) and insula (post-hoc test: df=67, t=3.92, p<0.01) as well as between the right IFG and middle frontal gyrus (MFG) (post-hoc test: df=67, t=4.64, p<0.01) (Figure 12).

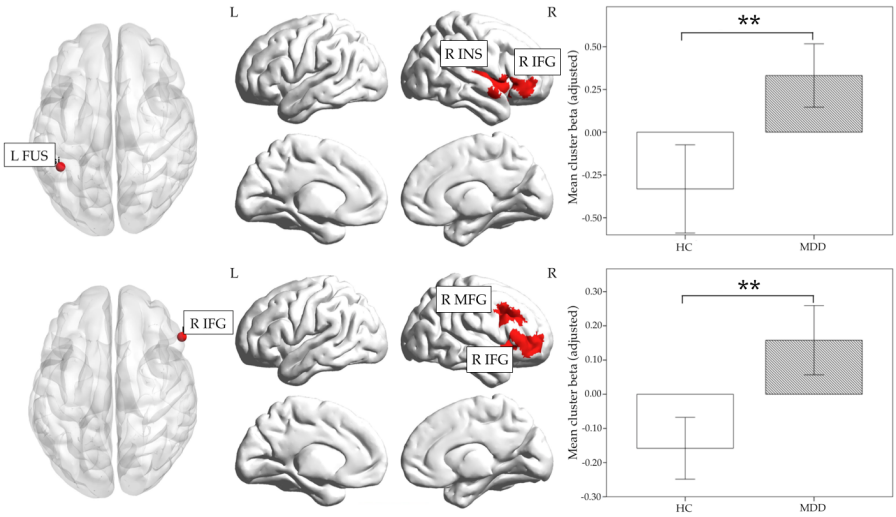

Figure 12 – gPPI results showing the main effect of group. Lateral and medial views display the result of our second level gPPI analysis across all subjects, showing each region of interest (spheres) that showed a significant effect of group with other brain regions (clusters) (p_{FWE}<0.05 at the cluster level following p<0.005 whole-brain voxel level). Bars show cluster mean beta values across all trials in each group adjusted for age and sex following linear regression (residuals). For post-hoc t-tests: p_{FDR}<0.05(*) and <0.01(**). Error bars are 95% confidence intervals. See Table 7 for seed abbreviations. MDD=depressed patients; HC=healthy controls; L=left; R=right; INS=insula; IFG=inferior frontal gyrus; MFG=middle frontal gyrus; FDR=false discovery rate.

11.3.4.7 *Two-way interactions: group*trial type and group*valence*

During SRT, patients had increased coupling between the left inferior frontal gyrus and the head of the left caudate nucleus compared to controls (post-hoc test: t=2.53, p_{FDR}=0.02). The same was observed concerning functional connectivity between the right inferior temporal gyrus and the precentral, postcentral and middle cingulate gyri (post-hoc test: t=2.59, p_{FDR}=0.02).

For ERT, on the other hand, coupling was reduced in patients between the same regions (post-hoc tests: t=-2.07, p_{FDR}=0.04 and t=-2.11, p_{FDR}=0.04 respectively).

Regardless of trial type, patients showed decreased coupling between the amygdala and the fusiform and lingual gyri during negative trials (post-hoc test: t=-3.07, p_{FDR}<0.01), and, to a lesser extent, increased coupling between these regions during positive trials (post-hoc test: t=2.10, p_{FDR}<0.05) (Figure 13).

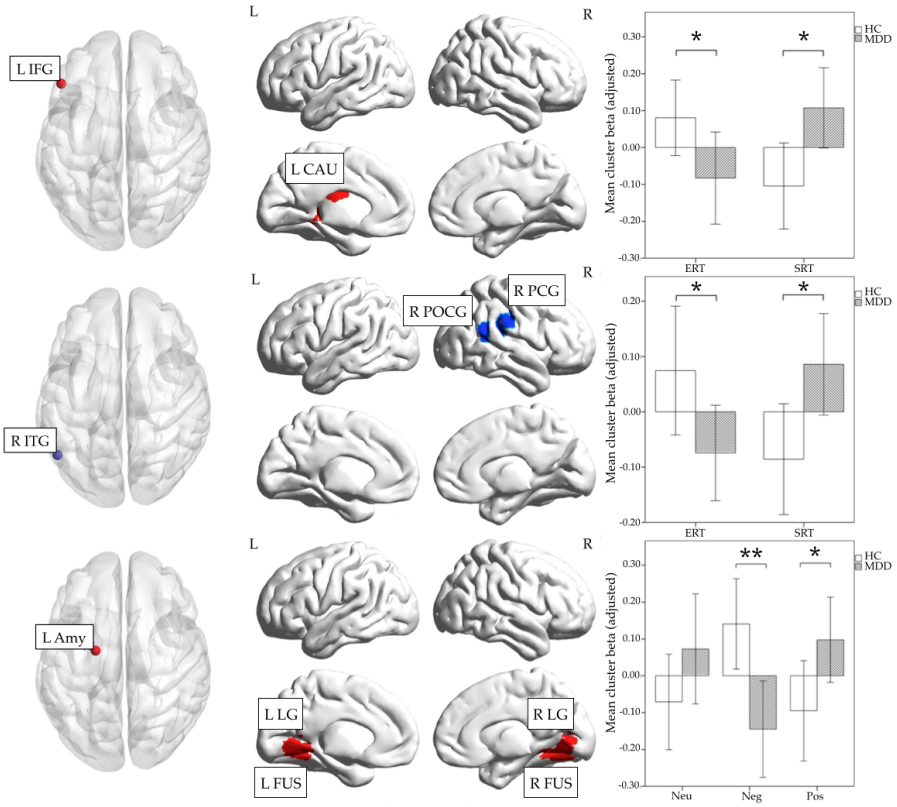

Figure 13 – gPPI results showing 2 way interaction effects. Lateral and medial views display the result of our second level gPPI analysis testing for group*trial type and group*valence interactions, showing each region of interest (spheres) that showed a significant interaction effect with other brain regions (clusters) (p<0.05 FWE at the cluster level following p<0.005 whole-brain voxel level). Bars show cluster mean beta values across all trials in each group adjusted for age and sex following linear regression (residuals). For post-hoc t-tests: p_{FDR}<0.05(*) and <0.01(**). Error bars are 95% confidence intervals. See Table 7 for seed abbreviations. MDD=depressive patients; HC=healthy controls' ERT=emotion recognition trials; SRT=shape recognition trials; Neu=neutral trials; Neg=negative trials; Pos=positive trials; L=left; R=right; CAU=caudate nucleus; POCG=postcentral gyrus; PCG=precentral gyrus; LG=lingual gyrus; FUS=fusiform gyrus; FDR=false discovery rate.

11.3.4.8 *Interaction between group, trial type and valence*

During SRT involving negative images (post-hoc test: df=67, t=-2.45, p_{FDR}=0.04) and ERT involving positive images (post-hoc test: t=-2.23, p_{FDR}=0.04), patients showed reduced coupling of the posterior cingulate cortex (PCC) and lingual gyrus. During shape evaluation of

positive stimuli, these regions also showed increased connectivity in the MDD group (post-hoc test: t=2.35, p_{FDR}=0.04).

Finally, in this latter trial type, patients also showed reduced functional connectivity between the sgACC and the superior frontal gyrus (post-hoc test: t=-2.66, p_{FDR}=0.02) (Figure 14).

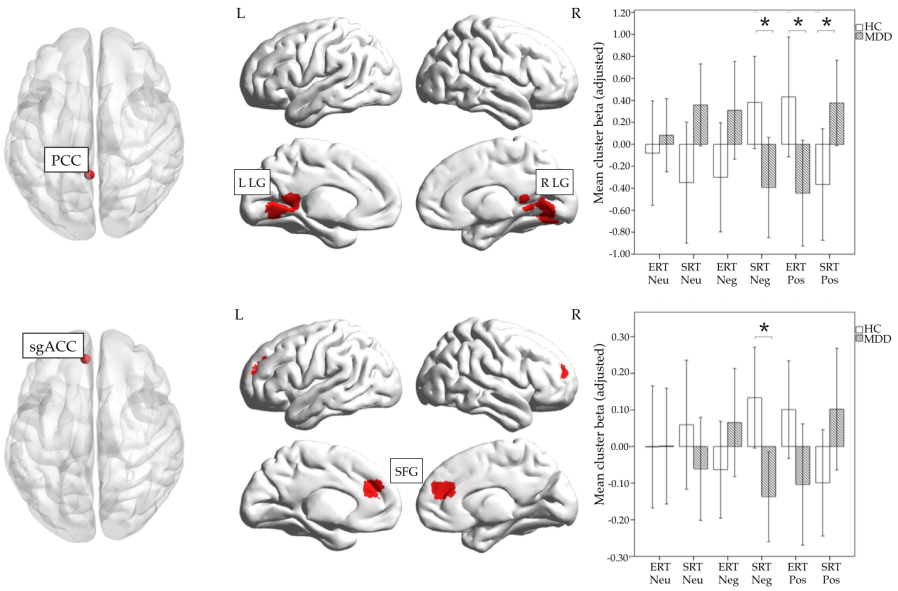

Figure 14 – gPPI results showing 3 way interaction effects. Lateral and medial views display the result of our second level gPPI analysis testing for group*trial type*valence interactions, showing each region of interest (spheres) that showed a significant interaction effect with other brain regions (clusters) (p<0.05 FWE at the cluster level following p<0.005 whole-brain voxel level). Bars show cluster mean beta values across all trials in each group adjusted for age and sex following linear regression (residuals). For post-hoc t-tests: p_{FDR}<0.05(*) and <0.01(**). Error bars represent 95% confidence intervals. See Table 7 for seed abbreviations. MDD=depressive patients; HC=healthy controls' ERT=emotion recognition trials; SRT=shape recognition trials; Neu=neutral trials; Neg=negative trials; Pos=positive trials; L=left; R=right; LG=lingual gyrus; SFG=superior frontal gyrus; FDR=false discovery rate.

11.3.5 *Correlational analysis*

We found a significant correlation between functional connectivity between the right IFG and MFG with the total number of hits in the patients group (r=0.45, p=0.01).

11.3.6 *Effect of medication*

We report no significant differences between medicated and unmedicated patients in the effects that showed a between groups difference (all tests $p>0.05$).

11.4 DISCUSSION

From a behavioural point of view, patients performed worse across all trials compared to controls. Their increased number of incorrect responses in ERT suggests an impaired ability to correctly identify the valence of emotional pictures, in line with previous findings of biased interpretation of stimuli in MDD (Murrough et al., 2011; Bylsma, Morris, and Rottenberg, 2008). Furthermore, patients also performed worse compared to controls in SRT, which might reflect a reduced ability to shift attention away from the content of the stimuli and, therefore, a deficit in voluntary emotional regulation (Gotlib and Joormann, 2010).

Reaction times were overall faster for negative and positive trials compared to neutral, suggesting faster attentional allocation to emotional stimuli, but were not different between the two groups.

Our results concerning BOLD responses to the different types of trials across groups add to the existing literature (see Table 6). Specifically, ERT showed a greater involvement of medial portions of prefrontal and posterior cingulate cortex, in line with their role in emotion generation, recognition and automatic regulation (Rive et al., 2013), whereas we report an involvement of dorsolateral prefrontal areas during SRT, comparable with their postulated role in voluntary emotional regulation (Rive et al., 2013). The involvement of structures such as the amygdala, insula and temporal lobes was also not surprising, since these regions have been extensively described as being recruited during emotional processing and also as being influenced by the valence of presented stimuli (Costafreda et al., 2008; Sergerie, Chochol, and Armony, 2008; Phan et al., 2002; Frank et al., 2014; Heinzel et al., 2005).

During SRT versus ERT, controls showed an increased activity in the anterior insula, whereas no difference was detected between the two trial types in patients. A reduced activation in this region in MDD has been shown in the past using paradigms eliciting cognitive processing of emotional stimuli, especially the ones involving recall (Sliz

and Hayley, 2012) and could be a by-product of a deficit in the engagement of working memory in the MDD cohort during our paradigm between the image and question presentation (Nagai, Kishi, and Kato, 2007; Young et al., 2012).

Our gPPI results have shown that, regardless of diagnosis, valence compared to shape recognition of emotional images involves greater coupling within an extensive functional network comprising the superior occipital, lingual and angular gyri, superior parietal lobules, lateral and medial portions of the frontal lobe as well as most portions of the cingulate cortex and the insula.

Patients, however, showed persistently increased functional connectivity across the two trial types between the fusiform gyrus and portions of this network, namely the IFG, inferior frontal sulcus and insula. Increased coupling of the fusiform gyrus in MDD has been reported before and ascribed to the functional hyper-connectivity of the default mode network in the disease (Karim et al., 2016). The anterior insula and frontal gyrus belong to the task positive network (Fox and Greicius, 2010), which might point to an overall hyper connectivity during our task in MDD between the default and task positive networks as well as within the latter. In light of the result of our correlation analysis, showing that patients with a higher connectivity within the task-positive network had a better overall performance, we believe that this finding could highlight a compensatory attempt to keep focused on the task. The altered interplay of these networks, however, might explain the overall performance deficit in our MDD cohort regardless of stimulus type.

Across SRT, regardless of valence, patients exhibited increased functional connectivity between the left IFG and the head of the left caudate nucleus. The caudate nucleus is thought to be one of the areas where emotional states and behaviours are initially generated (Phillips, Ladouceur, and Drevets, 2008). Increased connectivity between these areas might indicate that for MDD patients to successfully focus on the non-emotional aspects of a stimulus, a stronger top-down regulation of the regions originating the emotional response might be needed. Interestingly, during ERT connectivity between the same areas was reduced in patients, suggesting a deficit in top-down regulation while fully focused on the valence of emotional stimuli.

In SRT, we also detected higher connectivity in patients between the right inferior temporal gyrus (ITG) and the pre and post central gyri as well as the middle cingulate cortex, suggesting that stronger

coupling of the network of regions involved in emotional regulation with the ones involved in emotional recognition might be required for successful allocation of attention away from the emotional content as well. Similarly to what previously described, connectivity between these regions was also decreased in patients during ERT and could once again be related to a deficient regulation of the emotional response elicited by the pictures.

Concerning the main effects of valence, patients showed strong hypo-connectivity between the amygdala and visual areas during the evaluation of negative pictures, as well as hyper connectivity of the two structures while evaluating positive pictures. Coupling between the amygdala and the visual cortex has been hypothesised to mediate behaviour by enhancing sensory processing of affectively significant items (Pessoa and Adolphs, 2010). In depression, they have been found to be altered both in resting state (Cullen et al., 2014) as well as affect recognition tasks (Ho et al., 2014) and might be related to the biased processing of these stimuli characteristic of the illness.

Our analysis of the interaction between the valence, type and group effects revealed that the between group differences were especially prominent in trials either involving the voluntary attentional regulation of negative trials or the emotional recognition of positive trials. This is in line with both our finding of abnormal amygdala-visual cortex coupling as well as with the reports of biased interpretation of positive stimuli (Murrough et al., 2011; Bylsma, Morris, and Rottenberg, 2008) and impaired voluntary regulation of negative stimuli in depressed patients (Gotlib and Joormann, 2010).

Namely, patients showed a decreased connectivity between the PCC and visual regions in both these conditions, as well as decreased coupling between the subgenual and pregenual ACC while shifting attention away from the emotional content of negative stimuli. Impairment of PCC function has been hypothesised to be involved in deficits in attentional control and memory in MDD patients (Leech and Sharp, 2014), whereas the ACC has been often reported as an important centre of emotional regulation (Rive et al., 2013; Frank et al., 2014; Phan et al., 2002). The pregenual anterior cingulate cortex (pgACC), in particular, is specifically involved in the affective network and has been identified as being the main anterior cingulate association area, which mediates the interaction between the other, more specialized, sub-portions of the region, such as the sgACC (Yu et al., 2011). Its function is hypothesised to be crucial for emotional-cognitive interac-

tion (Yu et al., 2011). Therefore, our findings in MDD patients suggest that deficits in voluntary attentional regulation of negative stimuli and in valence interpretation of positive ones might be mediated by functional decoupling between and within areas involved in these processes.

Interestingly, we found PCC and visual regions to also be hyper-connected in patients during shape evaluation of positive stimuli. Once again, depressed patients showed changes in the processing not only of negative stimuli, but also of positive ones, which could be in line with their reported tendency to direct attention towards the first and away from the latter (Murrough et al., 2011).

It is necessary to address as a limitation the fact that most of the MDD patients were medicated, even with different drug classes. Therefore, even if we found no difference by investigating the effect of treatment with t-test on our functional effects comparing medicated and unmedicated patients, we cannot completely exclude that medication might play a role in our findings. We also wish to highlight the exploratory nature of our analysis: further studies are needed that could selectively target the functional alterations we have identified to link them to specific aspects of MDD.

11.5 CONCLUSION

To sum up, we confirm involvement of the ACC, superior frontal gyrus (SFG), PCC, amygdala, insula and temporal lobe during recognition of emotion across depressed and healthy subjects as well as increased functional coupling in these areas. Shift of attention away from the emotional content, on the other hand, activated lateral portions of the prefrontal cortex, the fusiform gyrus, cerebellum, occipital, temporal and parietal regions.

Behavioural performance was worse in MDD compared to controls across all trials, suggesting altered recognition and attentional regulation of emotion. Functionally, patients showed a reduced response during emotion regulation in the anterior insula, which could be related to a working memory deficit.

Overall, patients showed hyper-connectivity between and within the default mode and task positive networks. During voluntary emotional regulation, they had increased connectivity across areas involved in this process as well as with ones originating the emotional response. They also showed altered connectivity between the amyg-

dala and visual areas during the evaluation of negative and positive pictures, which might be related to biased valence processing.

Finally, the between group differences were especially prominent in trials either involving regulation of negative emotions or recognition of positive ones, showing decreased coupling between areas involved in attention allocation and emotional regulation.

12

FKBP5 SNP AND EMOTION PROCESSING AREAS

12.1 BACKGROUND

As outlined in Chapter 2, examples of the genes that have been investigated in MDD patients include ones involved in monoaminergic signalling such as the monoamine oxidase A (MAOA), tryptophan hydroxylase 1 (TPH1) (Gizatullin et al., 2006) and serotonin transporter (5-HTT) genes (Bellivier et al., 1998; Caspi et al., 2003; Frodl et al., 2010b). Mediators of neuronal plasticity have been studied as well, such as the brain derived neurotrophic factor (BDNF) (Arlt et al., 2013; Lavebratt et al., 2010) and BicC family RNA Binding Protein 1 (BICC1) (Bermingham et al., 2012) genes.

However, all genome-wide association analyses that have been performed have so far found inconclusive results regarding the association between SNPs in all these genes and MDD, suggesting that environmental factors may be crucial for developing the disease regardless of genetic vulnerability (Gyekis et al., 2013; Bosker et al., 2011; Clarke et al., 2010; Cohen-Woods, Craig, and McGuffin, 2013).

Compatible with the hypothesis of altered stress systems and immune response dysfunction in MDD (Miller, Maletic, and Raison, 2009), recent data has shown an association between the disease and allelic variants of genes involved in GR regulation.

The gene expressing FKBP5, in particular, is involved in the regulation of GR sensitivity (Scharf et al., 2011). The over expression of this protein can reduce hormone binding affinity and nuclear translocation of GR, down regulating the expression of anti-inflammatory proteins in neuronal nuclei (Wochnik et al., 2005). Genetic variants in this gene have been found to be suggestively associated with MDD (Gillespie et al., 2009), although not always achieving full statistical significance (Lavebratt et al., 2010). Furthermore, a study has also found an independent and interactive involvement of FKBP5 in antidepressant treatment response (Horstmann et al., 2010), emphasizing the potential clinical importance of this gene.

The rs1360780 SNP of the FKBP5 gene has been especially explored and its T allele has been reported as possibly associated with depres-

sion (Lavebratt et al., 2010; Gillespie et al., 2009). Further studies have revealed an association between this genotype and MDD in specific patient cohorts and the hypothesis has arisen that an increased risk of developing MDD in carriers of the T allele of rs1360780 could be present only following its interaction with a significant amount of chronic stress, such as the one undergone by gastric cancer patients (Kang et al., 2012) or victims of childhood maltreatment (Gillespie et al., 2009).

In the past few years, a significant association has also been reported between depression, FKBP5 allele T carrier status and an impaired regulation of the endocrine HPAA (Menke et al., 2013). Additionally, allelic differences in this gene have been found to be associated with alterations in cingulum anatomy measured using DTI in patients suffering from post traumatic stress disorder (PTSD), suggesting that it may have a role in determining white matter integrity and increased vulnerability for psychiatric disorders (Fani et al., 2014).

In order to better understand the way SNPs of FKBP5 may affect brain function, some studies have investigated if carriers of the high-risk T allele of rs1360780 responded differently to well-established fMRI paradigms. In healthy participants, the T allele of rs1360780 has been thus associated with an increase in BOLD responses in the hippocampus during a dot probe task, accompanied by alterations in hippocampal shape and with an attention bias toward threat (Fani et al., 2013; Holz et al., 2014). Another study has also found, in participants carrying the T allele, an association between increased activity in the dorsal amygdala during a face-recognition paradigm and self-reported childhood emotional neglect (White et al., 2012). Regarding depressed patients, on the other hand, the FKBP5 gene and childhood adversity have been shown to interact and to be associated with abnormal activity in the amygdala, hippocampus and orbitofrontal cortex (Holz et al., 2014).

All these findings support the hypothesis that there might be a neurobiological interplay between variants of the FKBP5 gene, stressful environmental factors (such as childhood adversity) and MDD, leading to specific changes in brain anatomy and function. Furthermore, during tasks eliciting emotional responses in patients, specific patterns may arise that differ between the genetically defined sub-samples.

The aim of our study was to investigate the differences in brain function and anatomy between patients affected by MDD and healthy controls in relation to the allelic variants of the rs1360780 SNP of the

FKBP5 gene. Furthermore, we wanted to investigate whether these differences might be explained by the interaction between the presence of the high-risk T allele of rs1360780 and environmental stress (in particular childhood adversity).

To achieve our goal, we employed fMRI during our emotion recognition task. By studying brain activity following the emotional evaluation of stimuli and that during assessment of their shape, we wanted to gain insight into the extent of emotional inhibition following the exposure to the stimulus: an ability that has been found impaired in depressed patients (see Chapter 11).

We then located areas presenting differences in activity during emotion and shape recognition between patients carrying the high-risk T allele and those being homozygous for the C allele. Next, we used DTI to assess whether these regions also presented morphological changes between these same two subgroups.

Finally, we have focused on the hypothesis that the genetic factor alone would not be sufficient to explain our morphological findings in depressed patients, but that its interaction with early life stress would highlight its contribution. Therefore, we have investigated the effects of the interaction of childhood adversity and rs1360780 allele status in explaining the DTI measures obtained by the use of a general linear model.

12.2 MATERIALS AND METHODS

12.2.1 *Sample*

The study was run on a subset of the CAMI dataset (see 7). It included 40 adult patients with MDD and 43 HC subjects.

12.2.2 *Rating Instruments*

Self and observer rated scales were also filled out for all participants (see Chapter 8 for details).

As measures of clinical severity, the HAMD (Hamilton, 1986) and BDI (Beck et al., 1961) were used.

The CTQ was also used to assess adversity during childhood and teenage years (Bernstein, D. P and Fink, L., 1998). The sum of its five sub-items (emotional, physical and sexual abuse, emotional and

physical neglect) was calculated and used as a continuous variable to evaluate the severity of childhood maltreatment for each participant.

12.2.3 *Genetic analysis*

See Chapter 9 for details on the genetic analyses.

All genotypes were found to be concordant with available online HapMapdata. All non-template samples returned a negative result. rs1360780 was in Hardy-Weinberg equilibrium (p>0.05) in this sample.

Our test SNP at FKBP5 has a minor allele frequency of 0.42 according to the University of California Santa Cruz Genome Browser. T is the minor allele and because homozygous TT samples were rare in our sample, we grouped them with heterozygous TC samples for analysis (T*).

12.2.4 *fMRI analysis*

See Chapter 10 for details on the fMRI sequence and task employed as well as for details on the analysis of hits and reaction times during the task.

12.2.4.1 *Preprocessing*

Data was analysed with SPM12 and preprocessed as described in Chapter 10.

After the motion correction step, 8 patients and 2 controls were excluded. Then co-registration of each participant's structural image to the mean of the motion corrected functional images, slice time correction, spatial normalization and smoothing using an 8 mm FWHM Gaussian kernel were applied.

12.2.4.2 *First level analysis*

The regressors entered in the first-level GLM analyses were the 6 time vectors of the questions' onsets and the 6 motion regressors. Then, t-tests were computed comparing ERT and SRT of each valence versus baseline.

12.2.4.3 *Second level analysis*

A 2*2*2*3 full-factorial model was set up in SPM12 on the resulting contrasts, where the first factor was diagnosis group (MDD or HC), the second factor was the presence of the T allele in the rs1360780 SNP of the $FKBP_5$ gene (T* or CC), the third factor was the trial type (ERT or SRT) and the fourth factor was its emotional valence (positive, negative or neutral), while age, gender and medication (entered as medication type: 0 for unmedicated patients and controls, 1 for SSRI and 2 for serotonin-norepinephrine reuptake inhibitors (SNRI)) were used as covariates.

A whole brain FWE correction with $p<0.05$ ($p<0.01$ for interaction testing) was performed in all comparisons to ensure statistical significance of our findings.

12.2.4.4 *Diffusion MRI analysis*

Data were pre-processed using ExploreDTI (http://www.exploredti.com), see Chapter 10 for details.

We reviewed the DTI data by visually inspecting the slice images. Head movement during scanning was less than 3 mm in x,y,z directions. After preprocessing, we used the "extract diffusion measures from atlas labels tool" in ExploreDTI, which warps each subject's image into standard space and defines masks for it based on the AAL atlas (http://qnl.bu.edu/obart/explore/AAL). These masks are then warped back into subject space and used for the extraction of DTI measures from the original images for each subject.

In particular, we compared MD and FA values of patients with the T allele of rs1360780 with those of patients homozygous for the C allele bilaterally in the anatomical areas where we found significant differences between the same groups during the fMRI task: insula and neighbouring rolandic operculum; Heschl gyrus; superior temporal lobe; parahippocampal gyrus; posterior cingulate cortex; inferior frontal gyrus, pars triangularis.

12.2.4.5 *Interaction modelling*

Within the MDD group, we defined and tested separate general linear models as implemented in SPSS Statistics version 22 (IBM) using each of our significant DTI findings as a dependent variable and, as an independent variable, the interaction between childhood maltreatment (CTQ scores) and the presence of the T allele of rs1360780. In

the model, age, sex and medication type were also included as confounds.

Statistics were considered to be significant when $p<0.0125$ considering testing for 4 different regions that were found to be significant in the fMRI and DTI analysis described above.

12.3 RESULTS

12.3.1 *Sample*

20 of the depressed patients and 22 of the healthy controls were found to be carriers of the T allele of rs1360780. There was no significant difference overall between participant groups regarding gender and age. CTQ scores were higher in patients ($p<0.01$) and controls showed a median total score close to the minimum posible of 25.

Among MDD patients, there were no significant differences between T* and CC participants regarding HAMD, BDI, illness duration, gender, childhood maltreatment and medication. T* patients were significantly older than CC patients ($t=2.31$, $p=0.03$). For a summary of demographics and clinical variables, see Table 10.

	HC		MDD		Test (p)
	T*	CC	T*	CC	
N	22	21	20	20	
Age (years)	36.00 ± 12.32	36.43 ± 14.65	45.35 ± 10.74	37.80 ± 9.91	F=2.67 (0.05)
Sex (F/M)	14/8	13/8	12/8	15/5	χ^2=1.21 (0.75)
HAMD	2 (0-15)	2 (0-6)	29 (14-45)	29 (17-40)	KW=56.44 (<0.01)
BDI	0 (0-9)	3 (0-15)	40 (3-53)	31 (22-59)	KW=55.98 (<0.01)
CTQ	28 (25-37)	32 (25-37)	38 (26-90)	38.50 (25-104)	KW=22.54 (<0.01)
Medication			6/7/7/0	4/8/8/0	χ^2=0.53 (0.77)
Illness duration (years)			10 (0.70-13.95)	18 (0.85-14.86)	U=0.03 (0.98)

Table 10 – Demographic and questionnaire scores. For parametric variables, mean and standard deviation are given. For non-parametric variables, the median as well as minimum and maximum values are given. Medication is expressed as none/SSRI/SNRI/other (antipsychotic or agomelatine) CTQ=childhood trauma questionnaire; HAMD=Hamilton rating scale for depression, BDI=Beck depression inventory; CTQ=childhood trauma questionnaire; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors.

12.3.2 *Behavioural analysis*

Concerning the number of hits, MDD performed worse across all trials (Wald χ^2=5.06, p=0.02) and we detected an interaction between diagnosis, trial type and valence (Wald χ^2=86.61, p<0.01). Analysis of individual trials showed that patients showed less hits especially in negative and positive ERT, as well as neutral and negative SRT (see Table 11).

Patients were slower to respond across all trials, regardless of type and valence (Wald χ^2=14.75, p<0.01, Table 11).

Allele status did not show any effect on number of hits or response times.

	HC		MDD		Wald χ^2 (p)
	T*	CC	T*	CC	
Hits ERT Neu	22.59 ± 3.52	21.24 ± 4.64	22.31 ± 4.36	24.25 ± 2.95	8.78 (<0.01)
Hits ERT Neg	26.36 ± 2.72	26.42 ± 4.10	24.81 ± 4.71	24.69 ± 5.45	1.41 (0.23)
Hits ERT Pos	27.68 ± 2.71	26.95 ± 2.35	24.00 ± 5.07	23.31 ± 3.88	16.28 (<0.01)
Hits SRT Neu	27.23 ± 2.51	26.62 ± 2.92	24.75 ± 3.40	25.94 ± 3.41	9.21 (<0.01)
Hits SRT Neg	26.59 ± 2.92	25.95 ± 2.67	24.12 ± 3.28	25.19 ± 2.07	3.91 (0.05)
Hits SRT Pos	27.91 ± 2.74	27.86 ± 2.33	25.00 ± 3.42	25.69 ± 4.42	3.45 (0.06)
RT ERT Neu (s)	0.93 ± 0.23	1.02 ± 024	1.14 ± 0.22	1.18 ± 0.30	8.11 (<0.01)
RT ERT Neg (s)	0.75 ± 0.24	0.91 ± 0.22	1.00 ± 0.22	1.02 ± 0.24	9.98 (<0.01)
RT ERT Pos (s)	0.63 ± 0.21	0.79 ± 0.21	0.87 ± 0.23	0.88 ± 0.31	8.77 (<0.01)
RT SRT Neu (s)	0.70 ± 0.20	0.82 ± 0.21	1.04 ± 0.31	0.99 ± 0.27	14.38 (<0.01)
RT SRT Neg (s)	0.73 ± 0.24	0.93 ± 0.23	1.15 ± 0.29	1.08 ± 0.26	20.84 (<0.01)
RT SRT Pos (s)	0.71 ± 0.20	0.83 ± 0.24	1.02 ± 0.31	0.97 ± 0.27	11.22 (<0.01)

Table 11 – Task performance. Tests show the results for our generalized estimation equations analysis. Overall effect of diagnosis on hits was significant across all trials (Wald χ^2=5.06, p=0.02). Test results for the effect of diagnosis are given. RT=reaction time; SRT=shape recognition trials; ERT=emotional recognition trials.

12.3.3 *fMRI*

For a summary of our fMRI results, see Table 12.

We found a significant interaction between genotype and diagnosis in the following areas: left and right superior parietal lobules; right frontal superior orbital gyrus; right frontal middle orbital gyrus; left middle occipital gyrus; left frontal inferior orbital gyrus; left insula and left superior temporal lobe.

CC controls showed, compared to CC patients, an increased response in the right middle frontal gyrus, in the left inferior frontal gyrus (pars triangularis) and in the left middle frontal gyrus, regardless of trial and valence. Conversely, T* controls compared to patients with the same genotype showed a greater activation in the right hippocampus, right precuneus, right lingual gyrus, left superior and inferior parietal lobules.

In response to emotional trials, CC patients showed an increased response compared to T* patients in the following regions: left superior temporal lobe and insula; left parahippocampal gyrus; left posterior cingulate cortex, precuneus and lingual gyrus. While judging the orientation of pictures, regardless of valence, they showed an increased response compared to patients carrying the T allele in the right inferior frontal gyrus, pars triangularis (Figure 15).

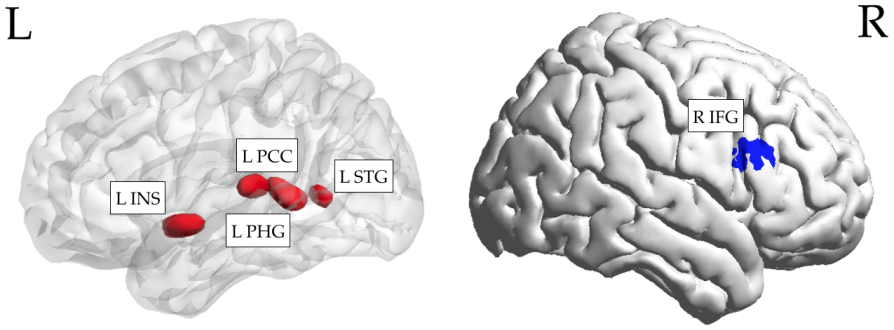

Figure 15 – Functional results of the contrast between patients carrying the T allele of rs1360780 and C homozygous patients. Areas of differential activation ($p<0.05$, whole-brain FWE corrected). Red=areas differentially active during emotional recognition trials; Blue=areas differentially active during shape recognition trials; L=left; R=right; INS=insula; PCC=posterior cingulate cortex; STG=superior temporal gyrus; PHG=parahippocampal gyrus; IFG=inferior frontal gyrus; FWE=family-wise error.

During ERT, CC controls had an increased response compared to T* controls in the left and right inferior orbital gyri and in the left and right middle frontal gyri. Similarly to patients, after SRT, they showed

an increased response compared to controls carrying the T allele in the left inferior frontal gyrus, pars triangularis.

Contrast	Voxels	Value (t or F)	Peak	Region
HC>MDD	116	6.05	39 41 2	R middle frontal gyrus
	107	5.58	24 -37 2	R hippocampus
		5.46	12 -49 5	R precuneus
		4.9	-18 -58 5	L lingual gyrus
	12	5.22	-30 -55 -1	L lingual gyrus
	12	4.81	30 35 29	R middle frontal gyrus
		4.66	39 35 32	R middle frontal gyrus
CC>T*	629	6.2	3 50 11	R anterior cingulate cortex
		5.74	21 47 26	R middle frontal gyrus
		5.72	33 41 23	R middle frontal gyrus
	157	5.87	-36 38 20	L middle frontal gyrus
		5.37	-33 35 -10	L inferior frontal orbital gyrus
		4.92	-30 29 8	L insula
	141	7.22	-21 -40 5	L hippocampus
	45	5.73	-3 -58 5	L posterior cingulate cortex
	36	5.39	-24 11 -13	L frontal superior orbital gyrus
	13	4.96	9 38 -13	R frontal medial orbital gyrus
FKBP5*group	1544	66.25	-24 -61 47	L superior parietal lobule

Contrast	Voxels	Value (t or F)	Peak	Region
		52.05	-45 -55 44	L superior parietal lobule
		50.33	18 -67 59	R superior parietal lobule
	51	65.07	18 41 -25	R frontal superior orbital gyrus
		41.56	33 38 -13	R frontal middle orbital gyrus
	48	39.05	-42 -67 5	L middle occipital gyrus
	32	32.92	-36 41 -4	L frontal inferior orbital gyrus
	24	35.81	-48 -22 11	L superior temporal lobe
	22	31.82	-39 5 -7	L insula
		29.31	-45 -4 -7	L superior temporal lobe
CC HC>CC MDD	338	5.79	30 35 29	R middle frontal gyrus
	160	4.9	-39 38 8	L inferior frontal gyrus pars triangularis
	45	5.89	-33 32 41	L middle frontal gyrus
		4.84	-39 35 29	L middle frontal gyrus
T* HC>T* MDD	192	6.39	27 -40 2	R hippocampus
		5.96	15 -46 5	R precuneus
		5.26	18 -61 -1	R lingual gyrus
	26	5.28	-24 -61 53	L superior parietal lobule
		5.26	-36 -55 53	L inferior parietal lobule

Contrast	Voxels	Value (t or F)	Peak	Region
CC MDD>T* MDD (ERT)	50	5.72	-42 2 -10	L insula
	49	5.44	-21 -46 2	L parahippocampal gyrus
	36	5.6	-45 -31 8	L superior temporal lobe
	26	5.37	-3 -58 5	L posterior cingulate cortex
CC MDD>T* MDD (SRT)	27	5.09	51 17 23	R inferior frontal gyrus
CC HC>T* HC (ERT)	375	6.9	-36 38 -7	L inferior orbital gyrus
		6.39	-33 38 17	L middle frontal gyrus
	280	5.96	33 35 -7	R inferior orbital gyrus
		5.15	27 38 -22	R middle frontal gyrus
CC HC>T* HC (SRT)	59	5.18	-39 35 11	L inferior frontal gyrus
		4.87	-39 38 -1	L inferior frontal gyrus pars triangularis

Table 12 – fMRI findings. Contrasts between groups are given, all p values are <0.05 whole brain family-wise error corrected. T*=carriers of the T allele of rs1360780. CC homozigous=C homozigous for the C allele of rs1360780; L=left; R=right.

12.3.4 *DTI*

For a summary of our DTI results, see Table 13. Since activity in the inferior frontal gyrus pars triangularis was found to differ during SRT between C homozygous participants and T allele carriers also in controls, we decided to study the DTI measures in this region in controls as well, but found no significant difference (p=0.15).

Increased MD values were found in patients carrying the T allele of rs1360780 compared to homozygous C patients in the left inferior frontal gyrus pars triangularis, left and right rolandic operculum, left and right insula, left and right Heschl gyrus.

Regarding FA values, we found them decreased in the left rolandic operculum and in the left insula. Comparisons between the two groups in the other regions of interest were not significant.

Region	MD (MDD)		Test (p)	FA (MDD)		Test (p)
	T*	CC		T*	CC	
L inferior frontal gyrus	$1.06*10^{-6}$	$0.98*10^{-6}$	t=2.55 (0.02)	$1.60*10^{-1}$	$1.61*10^{-1}$	t=-0.54 (0.59)
R inferior frontal gyrus	$0.96*10^{-6}$	$0.90*10^{-6}$	t=1.69 (0.10)	$1.53*10^{-1}$	$1.52*10^{-1}$	t=0.27 (0.79)
L insula	$1.02*10^{-6}$	$0.95*10^{-6}$	t=2.52 (0.02)	$1.58*10^{-1}$	$1.80*10^{-1}$	t=-2.27 (0.03)
R insula	$0.97*10^{-6}$	$0.91*10^{-6}$	t=2.19 (0.04)	$1.58*10^{-1}$	$1.71*10^{-1}$	t=-1.95 (0.06)
L Heschl gyrus	$1.11*10^{-6}$	$1.00*10^{-6}$	t=2.49 (0.02)	$1.52*10^{-1}$	$1.60*10^{-1}$	t=-1.03 (0.31)
R Heschl gyrus	$1.10*10^{-6}$	$1.00*10^{-6}$	t=2.73 (<0.01)	$1.11*10^{-1}$	$1.15*10^{-1}$	t=-0.77 (0.45)
L posterior cingulate gyrus	$0.87*10^{-6}$	$0.84*10^{-6}$	t=1.05 (0.30)	$2.82*10^{-1}$	$2.70*10^{-1}$	t=0.53 (0.60)
R posterior cingulate gyrus	$0.85*10^{-6}$	$0.82*10^{-6}$	t=0.86 (0.40)	$3.80*10^{-1}$	$3.59*10^{-1}$	t=0.70 (0.49)
L parahippocampal gyrus	$0.93*10^{-6}$	$0.92*10^{-6}$	t=0.27 (0.80)	$2.01*10^{-1}$	$2.00*10^{-1}$	t=0.16 (0.87)
R parahippocampal gyrus	$0.89*10^{-6}$	$0.89*10^{-6}$	t<0.01 (1.00)	$1.92*10^{-1}$	$1.96*10^{-1}$	t=-0.82 (0.42)
L rolandic operculum	$1.03*10^{-6}$	$0.93*10^{-6}$	t=3.36 (<0.01)	$1.59*10^{-1}$	$1.79*10^{-1}$	t=-3.59 (<0.01)
R rolandic operculum	$0.90*10^{-6}$	$0.85*10^{-6}$	t=2.51 (0.02)	$1.67*10^{-1}$	$1.73*10^{-1}$	t=-1.13 (0.27)

Table 13 – DTI findings. The results of t-tests for the contrasts between C homozygous patients and T allele carrier patients for rs1360780 are given, in each region that we tested. MD is expressed in 10^{-3} mm^2s^{-1}. L=left, R=right.

12.3.5 *Interaction modelling*

For a summary of our significant models, see Table 14.

Dependent variables used in our models were normally distributed (Kolmogorov-Smirnov test $p>0.05$). Diagnostic procedures were run on all linear models to ensure a good fit of the data, including standardised and non-standardised residual plotting and marginal model plots.

Our model yielded a successful and valid fit, with the interaction between rs1360780 allele status and CTQ scores being the only significant predictor, for the left and right insula MD, the left rolandic operculum MD and FA and for the left frontal inferior gyrus, pars triangularis, MD. After correcting for multiple comparisons, the interaction was still significant for the left rolandic operculum, both for MD and FA. Interestingly, the counfounding effects age and sex did not show a predictive effect of MD and FA (Figure 16).

These models did not achieve a significant fit if the main effects of CTQ scores and rs1360780 allele status were entered as separate, non-interacting variables. In all other regions of interest, the interaction between CTQ scores and rs1360780 allele status did not show any significant role in predicting DTI measurements.

None of the independent variables included in our models were successful at explaining the functional responses measured in any of the clusters. We have also tested with an analogous general linear model the possible role of CTQ scores in predicting amygdalar responses to negative emotional stimuli, as reported from previous literature in healthy controls (Dannlowski et al., 2012). However, we do not report any significant fit both for negative cognitive and emotional trials ($p>0.50$).

Effect	L insula MD	R insula MD	L rolandic operculum MD	L rolandic operculum FA	L inferior frontal gyrus MD
Sex	F=0.85 (0.36)	F=0.01 (0.92)	F=0.17 (0.69)	F=0.20 (0.66)	F<0.01 (1.00)
Medication	F=0.61 (0.55)	F=0.26 (0.77)	F=0.83 (0.44)	F=0.89 (0.42)	F=0.01 (0.99)
Age	F=3.01 (0.09)	F=2.70 (0.11)	F=1.38 (0.25)	F=0.01 (0.92)	F=3.33 (0.77)
rs1360780*CTQ	F=3.58 (0.04)	F=4.51 (0.02)	F=5.74 (<0.01)*	F=5.92 (<0.01)*	F=3.12 (0.05)

Table 14 – Results of our general linear models in depressed patients. For each region in which we found significant results, the F or t values and p are given for the fit of the overall model and of each factor. rs1360780*CTQ=interaction between allele status and childhood trauma questionnaire scores. L=left, R=right, MD=mean diffusivity, FA=fractional anisotropy. *Significant findings after family-wise error correction (p<0.0125).

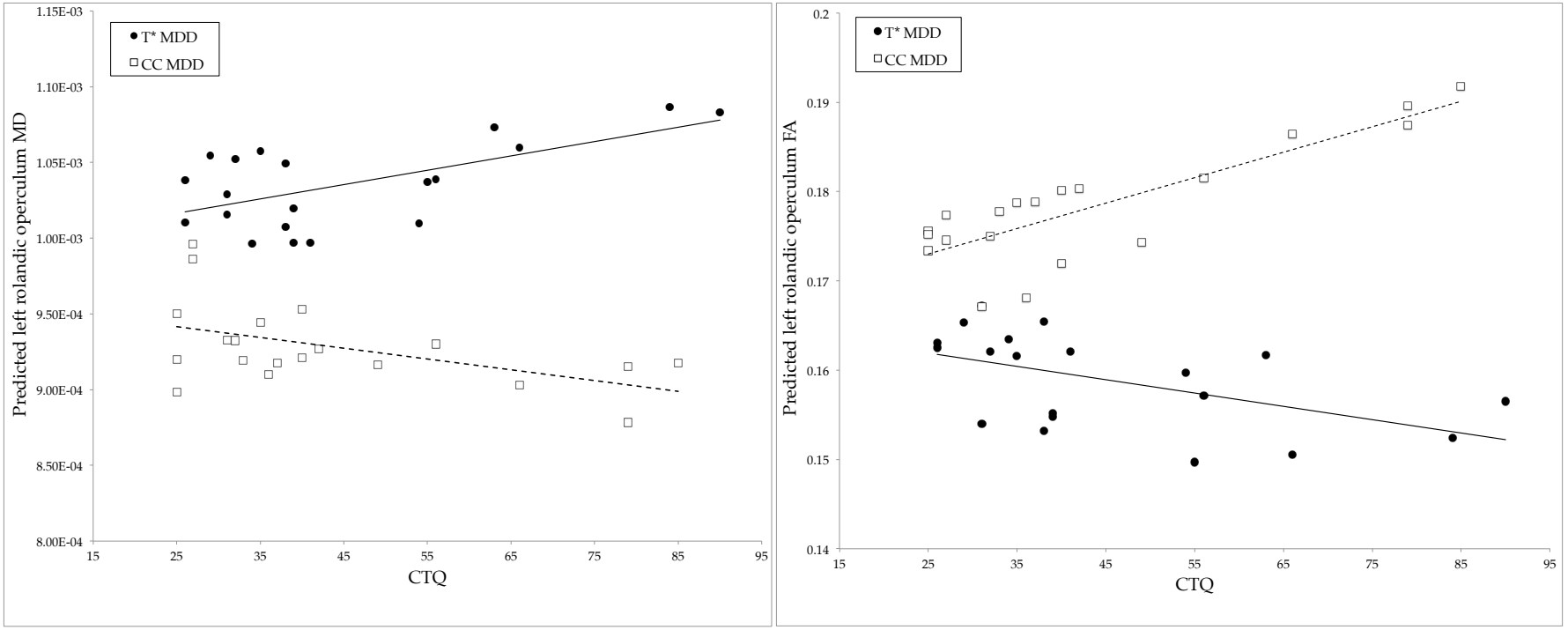

Figure 16 – Mean diffusivity (MD) and fractional anisotropy (FA) values in the left rolandic operculum in depressed patients as predicted by the Childhood Trauma Questionnaire (CTQ) in our general linear model. CTQ has proven to be the only significant predictor of MD and FA values in this region, also surviving multiple comparisons testing. Its effect shows an interaction with the genotype of patients, with the difference between the two genotypes becoming more apparent the higher the CTQ score of the patient. MD is expressed in 10^{-3} mm^2s^{-1}.

Our task was successful in highlighting differences between patients with MDD and healthy controls by showing a decreased response to emotional stimuli for patients in several areas that have already been extensively reported in the literature, such as the hippocampus and temporal lobe, the prefrontal cortex and the posterior cingulate (see Fitzgerald et al., 2008).

These areas were overall hypoactive in response to emotional stimuli in our participants carrying the T allele of rs1360780, suggesting that this gene may indeed have an impact on areas relevant for the disease even in healthy controls. Animal studies found the FKBP5 gene to be especially expressed in some of these regions, such as the hippocampus (Scharf et al., 2011) and recent studies have shown the impact of rs1360780 polymorphism on both anatomy and function of this area in healthy subjects (Fani et al., 2013; Fani et al., 2014).

Moreover, a significant interaction between diagnosis and allele status, mainly located in the superior temporal and parietal lobes, in the orbitofrontal gyri and in the insula was found. The functional differences in these areas could be exacerbated in the presence of both the disease and the T allele of rs1360780. Regarding the insula and superior temporal lobe, these regions have been found in MDD patients to consistently show a decreased activity during resting state studies, a relative lack of activation during induction of negative affect and an increase in activation with SSRI treatment (Fitzgerald et al., 2008). Furthermore, the volume of the insular cortex has been found to be negatively correlated to clinical symptoms in a sample of MDD patients (Sprengelmeyer et al., 2011).

In our study, patients carrying the high risk T allele demonstrated significantly reduced activity in the insula following emotional stimuli than CC homozygous patients. The same was not observed for controls, suggesting that the effect of rs1360780 on the insula's function could become apparent when additional factors come into account that are related to the disease. One such factor could be childhood maltreatment, that was significantly more pronounced in our patients with MDD compared to controls. This finding is consistent with the fact that the insula appears to deactivate in response to the acute activation of the stress hormone axis (Pruessner et al., 2008), such as the presentation of emotionally stressful material in our task. Genetic regulation of GR function together with the imbalances of the

HPAA characteristic of depression could explain how insular activity differs between subsets of patients.

Controls, on the other hand, exhibited differences in the middle and inferior frontal and orbitofrontal gyri that mimic more closely our findings from the overall contrast between allelic groups regardless of diagnosis. The same could be said for the reduced activation in the inferior frontal gyrus pars triangularis that we observed in both patients and controls carrying the T allele of rs1360780, especially during geometrical trials. This area is indeed specifically involved in cognitively challenging tasks, such as our geometrical trials, and its function has been found to be impaired in depressed patients (Harvey et al., 2005).

There have been many reports of an altered function in the amygdala in MDD during emotional processing (Sheline et al., 2001; Siegle et al., 2007; Victor et al., 2010; Suslow et al., 2010; Stuhrmann, Suslow, and Dannlowski, 2011) but we did not see any effect in this region in our analysis. This could be due to a number of reasons. For example, we have considered brain activity in response to a task where the patient was asked to assess emotional content or geometrical shape of a picture. Therefore, the focus of our present analysis was on the cognitive processing following the question and being attentional control of emotion a core component of this task, we were mainly expecting an involvement of cortical regions. Also, most studies reporting abnormal amygdalar activation in depression and investigating their links with other factors (such as childhood trauma) have used tailored tasks designed to elicit strong responses in this area, such as tasks involving emotionally salient faces (Sheline et al., 2001; Victor et al., 2010; Suslow et al., 2010; Siegle et al., 2007; Dannlowski et al., 2007; Dannlowski et al., 2012; Stuhrmann, Suslow, and Dannlowski, 2011). It is possible that our study design, which was focused on an exploratory investigation of the interaction between disease, brain function, structure and a high-risk genotype, did not have enough power to investigate activation in such a small region.

DTI demonstrated that MD values in the insula and neighbouring temporal regions are significantly different between patients carrying the T allele of rs1360780 and those homozygous for the C allele. FA results, on the other hand, achieved significance in the left rolandic operculum and insula, confirming a difference in microstructural properties of these areas.

Increased MD and reduced FA have been found to be associated with axonal degeneration, demyelination, decreased axonal density and incomplete white matter maturation (Alexander et al., 2011; Feldman et al., 2010). In healthy controls, the T allele of rs1360780 has been found to be associated with structural abnormalities in the white matter (Fani et al., 2014) and changes such as these have been reported in patients with MDD as well (Frodl et al., 2012; Frodl et al., 2011; Ugwu et al., 2014). Specifically, two studies (Abe et al., 2010; Shimony et al., 2009) reported higher MD and lower FA scores in the white matter of the prefrontal cortex. Our findings suggest that the high-risk T allele of rs1360780 (and subsequent modifications in stress hormone axis function) might have an impact on the diffusional properties of the grey matter of these areas as well. This might be due to changes in axonal organization or maturation. Such changes, in turn, might overlap with those associated with clinical depression and therefore become more evident and be related to the altered function we have found in the same regions.

Finally, we would like to point out how, in our patient group, the interaction between childhood abuse and genotype of rs1360780 successfully explained MD scores in the left insula, in the left and right rolandic operculum and in the left inferior frontal gyrus, as well as FA in the left rolandic operculum. After correction for multiple comparisons, our finding was still significant in the left rolandic operculum, both for MD and FA. This is consistent with previous literature on the role of the allelic variants of FKBP5: a stressful environment achieves phenotypical relevance towards the modification of the stress hormone axis only in combination with the allelic variant, with childhood maltreatment having an especially significant impact (Binder et al., 2008; Ising et al., 2008).

This study presents some noteworthy limitations. First of all, due to the rarity of the T allele, we were forced to group homozygous and heterozygous patients together to achieve a sufficient group size. The sample overall is still small for a genetics study in each of the groups, but our choice of this SNP was guided by previous consistent literature documenting findings in large samples. Patients carrying the T allele of rs1360780 were older than CC ones. We used age as a covariate in all our linear models and those did not show a significant prediction of MD and FA in our regions of interest, but we cannot exclude that this difference might confound our results pertaining the MDD group. Also, it is still unclear how rs1360780 might influence

brain activity in the reported regions. Since the GR receptor is ubiquitously expressed, the relationship between the brain areas involved in emotional regulation and the T allele of rs1360780 is likely to be extremely complex and still needs to be elucidated. Further studies are therefore needed to confirm our findings in a larger sample and in respect to possible molecular mechanisms of rs1360780 action. Also, we could not take many other factors into consideration that might have been associated with MDD, such as family history or environmental variables besides childhood maltreatment. Furthermore, it is unclear how low levels of FA such as the ones we detected might be related to grey matter microstructure. Future studies should investigate the white matter fiber tracts that connect the regions that we found to be differentially active depending on rs1360780. Finally, many of our MDD patients were medicated and, although no significant difference in medication was found between the two genetically defined subgroups of patients and medication was used as a covariate in our functional analysis, we cannot completely exclude that some of the differences we reported between patients and controls might be due to this factor.

12.5 CONCLUSION

In summary, we showed for the first time that allelic variants in the rs1360780 region of the FKBP5 gene are associated with differences in regional brain activity during evaluation of emotional stimuli in patients with MDD. Furthermore, these differences are mirrored by changes in diffusional properties of the grey matter in the same regions. These are in turn explained by the interaction between allele status of rs1360780 and the amount of maltreatment during childhood.

Therefore, our findings provide further evidence that genetic variation in GR function, especially when coupled with a chronically stressful environment in early life, might impact on brain structure in regions involved with emotional processing, thus affecting brain function and possibly leading to an increased vulnerability for MDD.

13

FKBP5 METHYLATION AND EMOTION PROCESSING AREAS

13.1 BACKGROUND

Our results outlined in Chapter 12 have shown that the rs1360780 SNP of *FKBP5* plays a role in mediating the effects of childhood maltreatment on brain structure and function.

How exactly chronic stress might influence *FKBP5* transcription and its protein function is not known, but it has been suggested that their interplay might be mediated by epigenetic mechanisms (Tyrka, Ridout, and Parade, 2016; Provencal and Binder, 2015). In support of this view, treatment of human hippocampal progenitor cells with glucocorticoids induced long-lasting demethylation of FKBP5 regulatory intronic regions and increased its expression. This suggests that prolonged cortisol exposure may lead to demethylation at FKBP5 intronic regions in cells, including multipotent neuronal cells (Klengel et al., 2013). Recent work has expanded this finding to human populations by showing that exposure to chronically high cortisol levels in Cushing syndrome was associated with lower DNA methylation level of FKBP5 introns assessed in white blood cells (Resmini et al., 2016). Decreased methylation was also observed in DNA taken from saliva samples of maltreated children (Tyrka et al., 2015) and in whole blood and saliva samples of adult victims of childhood trauma (Klengel et al., 2013). However, other studies have shown increased rather than lower intronic FKBP5 methylation levels following current and past chronic stress (Needham et al., 2015; Yehuda et al., 2016). Therefore, current findings suggest that methylation levels at regulatory regions might constitute a link between FKBP5 expression and both endocrine as well as environmental stress, although the directionality of their correlation remains uncertain.

It is also still unclear which role FKBP5 might play in the structural and functional brain differences detected between MDD patients and HC. As outlined in Chapter 12, several MRI studies have investigated grey matter volume, white matter integrity and neural responses to stimuli in patients carrying high-risk allele variants of

FKBP5 rs1360780 SNP relative to individuals without a risk allele, highlighting structural and functional differences in brain areas involved in emotional processing (Hirakawa et al., 2016; Fujii et al., 2014; Tozzi et al., 2015; Fani et al., 2014; Holz et al., 2014; White et al., 2012). None of them, however, took into account epigenetic modifications of the gene.

After conducting a study assessing rs1360780, *FKBP5* epigenetics, exposure to early chronic stress and hippocampal volume, Klengel et al., 2013 provided the first evidence for a comprehensive model in which allelic status leads to differences in the transcription of *FKBP5* in response to glucocorticoid receptor activation after childhood maltreatment. These changes would in turn lead to *FKBP5* intron demethylation and volume decrease in the hippocampus. Similarly, Resmini et al., 2016 also found smaller hippocampal volumes in association with lower methylation level of FKBP5 introns 2 and 7 in Cushing syndrome patients. The first study investigating the interaction of MDD, FKBP5 allele status, methylation and grey matter changes in depressed patients has only recently been conducted (Han et al., 2017). In this work, the T allele of rs1360780 was associated with volume reduction of portions of the frontal and parietal cortex, but exclusively in patients. Interestingly, an effect of FKBP5 methylation on right frontopolar gyrus grey matter thickness was detected in participants regardless of diagnosis, but dependent on rs1360780 allelic status. Overall the authors provide further evidence that rs1360780 and MDD have interactive effects on gray matter volumes of cortical regions involved in emotion processing and mood regulation. In addition to this, FKBP5 methylation might predict changes in the structure of these areas depending on rs1360780.

To our knowledge, no studies have yet assessed whether structural changes associated with FKBP5 allelic status and methylation also predict functional ones in the same regions. Furthermore, childhood adversity has been shown to play a role in FKBP5 methylation and to interact with rs1360780 in predicting changes in brain structure and function (Gillespie et al., 2009; Tozzi et al., 2015; Klengel et al., 2013). These interactions have not yet been explored in MDD, as highlighted by Han et al. as a limitation of their study (Han et al., 2017).

Our goal was therefore to investigate, in MDD patients and HC, the relationship between epigenetic modifications in *FKBP5* with allelic status of rs1360780, exposure to childhood adversity and structural as well as functional brain measures.

Since Resmini et al., 2016 found more pronounced effects at CG-6 and CG-7 in the intron 7 region of *FKBP5* (rs1360780 is located in intron 2), we limited our analyses to these two sites, which are in or close proximity to a glucocorticoid response element (GRE) (see supplementary figure 2 in ref. Klengel et al., 2013). We investigated the methylation level of these CG-sites in whole blood DNA samples, expecting to find lower mean methylation levels in MDD patients expressing the T allele of rs1360780 and exposed to childhood abuse, compatibly with (Klengel et al., 2013).

We then acquired structural MRI scans of our participants as well as functional ones during an emotion recognition task that consistently showed activation in emotional processing areas in the past (Lisiecka et al., 2011; Tozzi et al., 2015; Tozzi et al., 2016). We used a ROI approach, targeting parts of the brain that are known to be involved in emotion recognition and to be especially affected in MDD, in particular the medial and lateral prefrontal cortex, amygdala, insula and hippocampus (Phillips, Ladouceur, and Drevets, 2008; Drevets, Savitz, and Trimble, 2008). We hypothesized that lower whole blood *FKBP5* methylation would also be correlated with lower grey matter content in some of these areas (Klengel et al., 2013; Han et al., 2017). We then investigated correlations of FKBP5 methylation and brain hemodynamic responses selectively in regions where it predicted grey matter concentration.

Finally, we assessed if the regions whose activity and grey matter concentration were correlated with *FKBP5* methylation were also relevant for depression psychopathology, by comparing them between MDD and HC and by correlating their function with measures of symptoms severity.

13.2 MATERIALS AND METHODS

13.2.1 *Sample*

The study was run on a subset of our complete dataset, comprising participants from the CAMI and TCIN sites (see Chapter 7). It included in total 60 adult patients with MDD and 56 HC.

13.2.2 *Rating Instruments*

Self and observer rated scales were also filled out for all participants (see Chapter 8 for details).

As measures of clinical severity, the HAMD (Hamilton, 1986) and BDI (Beck et al., 1961) were used.

The CTQ was also used to assess adversity during childhood and teenage years (Bernstein, D. P and Fink, L., 1998). The sum of its five sub-items (emotional, physical and sexual abuse, emotional and physical neglect) was calculated and used as a continuous variable to evaluate the severity of childhood maltreatment for each participant.

13.2.3 *Genetic analysis*

See Chapter 9 for details on the genetic and epigenetic analyses.

All genotypes were found to be concordant with available online HapMapdata. All non-template samples returned a negative result. rs1360780 was in Hardy-Weinberg equilibrium ($p>0.05$) in this sample.

Our test SNP at *FKBP5* has a minor allele frequency of 0.42 according to the University of California Santa Cruz Genome Browser. T is the minor allele and because homozygous TT samples were rare in our sample, we grouped them with heterozygous TC samples for analysis (T*).

13.2.4 *Demographic and clinical measures*

All statistical analyses were conducted using SPSS version 22 (IBM Corp). Demographic variables and clinical test scores were compared between MDD and controls using independent t-tests (age, methylation percentage), chi-square tests (sex, rs1360780) and Mann-Whitney U tests (CTQ, HAMD, BDI). The same tests were also conducted to compare participants based on the site and rs1360780 variables (Table 16).

13.2.5 *Predictors of FKBP5 methylation*

We entered *FKBP5* methylation percentage as dependent variable in a full factorial GLM that had the following independent variables: diagnosis (binary: HC or MDD), site (binary: CAMI or TCIN), sex (binary:

male or female), rs1360780 (binary: CC or T*), age (continuous), CTQ total score (continuous) as well as all 4 possible interactions between rs1360780 allele status, diagnosis and CTQ total score. Upon identification of significant interactions, the post-hoc models were rerun splitting the data for the interacting factors. Within the MDD group, medication was added as a binary factor (medicated, unmedicated).

13.2.6 *Magnetic resonance imaging*

See Chapter 10 for details on the fMRI sequence and task employed as well as for details on the analysis of hits and reaction times during the task.

13.2.6.1 *Preprocessing*

Data was analysed with SPM12 and preprocessed as described in Chapter 10.

After motion correction of the fMRI data, 4 patients and 3 controls were excluded from the sample, resulting in a final size of 50 controls and 56 MDD patients.

13.2.6.2 *Voxel-based morphometry*

The segmentation pipeline of CAT12 was run on all T1 images using default parameters to obtain MNI normalized and modulated structural segmented data for all subjects as outlined in Chapter 10.

Warping fields for the forward transformation to MNI space were saved and then applied to the functional data of each corresponding subject. The anatomical images passed quality control as provided by CAT12 and the sample was homogeneous. TIV was also estimated and saved for each subject for subsequent VBM.

13.2.6.3 *First level analysis*

A first-level GLM analysis was conducted on the normalized functional data, using a canonical HRF as response function and a high-pass filter of 128 s. Our 6 regressors of interest (times at which the questions were presented) were entered in the GLM along with the 6 motion parameters of each subject.

T-tests were then conducted on ERT>SRT first-level contrasts for each emotional valence (neutral, negative and positive), thus repre-

senting brain response to the evaluation of each emotion elicited by the pictures in comparison to that of their shape.

13.2.6.4 *ROI definition*

The AAL (Maldjian et al., 2003) as provided in the CAT12 toolbox, was used to identify the following emotional processing structures (left and right): superior frontal gyrus, superior frontal orbital gyrus, middle frontal gyrus, middle frontal orbital gyrus, inferior frontal operculum, inferior frontal gyrus, inferior frontal orbital gyrus, superior medial frontal gyrus, medial frontal orbital gyrus, insula, anterior cingulum, hippocampus and amygdala, for a total of 13 ROIs on each side (see Table 15 for ROI details).

Mean activity change from the first level ERT>SRT contrast for each emotional valence, as well as the mean grey matter concentration were extracted for each of the ROIs. These values and estimated total intracranial volume were then entered into SPSS Statistics version 22 (IBM Corp) for statistical analysis.

Region	Name	Volume (mm^3)	Centre
L superior frontal gyrus	L SFG	26.23	-19 33 40
R superior frontal gyrus	R SFG	28.57	19 31 42
L superior frontal orbital gyrus	L SFOG	7.65	-18 44 -15
R superior frontal orbital gyrus	L SFOG	7.24	15 45 -16
L middle frontal gyrus	L MFG	37.04	-35 29 33
R middle frontal gyrus	R MFG	38.81	36 32 34
L middle frontal orbital gyrus	L MFOG	6.54	-31 47 -11
R middle frontal orbital gyrus	R MFOG	7.76	29 52 -12
L inferior frontal operculum	L IFO	7.67	-47 10 13
R inferior frontal operculum	R IFO	9.11	48 14 18
L inferior frontal gyrus	L IFG	17.18	-45 28 9
R inferior frontal gyrus	R IFG	15.39	46 30 11
L inferior frontal orbital gyrus	L IFGO	12.59	-35 28 -15
R inferior frontal orbital gyrus	R IFGO	13.09	37 31 -14
L superior medial frontal gyrus	L SMF	21.33	-7 47 29
R superior medial frontal gyrus	R SMF	15.30	6 49 28
L medial frontal orbital gyrus	L MFO	4.83	-7 51 -11
R medial frontal orbital gyrus	R MFO	6.23	5 49 -10
L insula	L INS	12.70	-36 2 1
R insula	R INS	12.19	36 3 1
L anterior cingulate	L ACC	10.37	-5 33 11
R anterior cingulate	R ACC	9.68	7 35 15
L hippocampus	L HIP	7.03	-25 -24 -12
R hippocampus	R HIP	6.74	27 -23 -12
L amygdala	L AMY	1.56	-25 -5 -19
R amygdala	R AMY	1.64	24 -4 -20

Table 15 – ROIs used for the analysis. For each region of interest we selected from the automatic anatomical labeling atlas, the following characteristics are shown: abbreviation, name, number of voxels, volume in mm^3 and centre Montreal Neurological institute coordinates.

13.2.6.5 *Effect of FKBP5 methylation on brain structure and function*

First, we ran a model for each of our 13 ROIs as follows. GM concentration was set as dependent variable (continuous). To limit the number of models in analyses, since we did not expect strongly lateralized effects of blood FKBP5 methylation percentage, we added the within-subject variable "ROI side" (factor with 2 levels: left and right) to the model. Between subjects independent variables were age, site, sex, rs1360780, diagnosis, FKBP5 methylation percentage and TIV (continuous). All main effects as well as all possible interactions between FKBP5 methylation, diagnosis and rs1360780 were tested using Wald

χ^2 tests, considering significant a p<0.05 FDR corrected for multiple comparisons (Benjamini, 2010).

We then assessed fMRI changes in our ROIs. First of all, to confirm that they showed significant BOLD activity in our experimental conditions, we conducted one-sample t-tests on their mean ERT>SRT response across all participants and excluded ROIs for which there was no significant activation (p>0.05). Then, we conducted another generalized estimating equations (GEE) analysis, defining activation as measured by our contrast values as dependent variable (continuous). Independent within-subject variables were ROI side and, since we did not expect correlates of blood FKBP5 methylation to be valence-specific, emotional valence (factor with 3 levels: neutral, negative and positive). Between subjects independent variables were site, age, sex, diagnosis, rs1360780 and FKBP5 methylation percentage. As before, all main effects as well as all possible interactions between FKBP5 methylation, diagnosis and rs1360780 were tested, considering significant a p<0.05 FDR corrected for multiple comparisons (Benjamini, 2010).

Finally, since we found a main effect of diagnosis for inferior frontal gyrus pars orbitalis (IFGO) activation, we tested whether this was predicted by symptoms severity within the MDD group using a GEE model including independent variables site, age, sex, medication, rs1360780 and BDI total score and HAMD total score (continuous) respectively.

13.3 RESULTS

13.3.1 *Demographics and behavioural*

Demographic information of our samples along with questionnaire scores and tests are summarised in Table 16. CTQ scores were higher in patients (p<0.01) and controls showed a median total score close to the minimum possible of 25. No differences were detected regarding mean age or sex and T allele distribution between patients and controls (all tests p>0.05). Methylation of the FKBP5 intron 7 CG-6 and CG-7 sites were strongly correlated (r=0.56, p<0.01). Methylation levels in T* participants (mean=61.15 ± 4.27) and those in CC participants (mean=60.53 ± 3.66) were not significally different (t=0.78, p=0.33). Smokers had comparable methylation levels to non-smokers (t=0.80, p=0.94). Data from the two sites did not significantly differ for age, mean FKBP5 intron methylation, sex, number of smokers,

rs1360780, CTQ, HAMD and BDI. The same was true for T* and CC participants (all tests $p>0.05$).

	CAMI		TCIN		Test (p)
	HC	MDD	HC	MDD	
N	29	31	21	25	
Age (years)	38.28 ± 12.40	40.42 ± 9.72	34.00 ± 11.63	37.76 ± 13.17	F=1.26 (0.29)
Sex (F/M)	17/12	21/10	13/8	15/10	χ^2=0.61 (0.89)
Smoking (yes/no)	5/24	8/23	3/18	8/17	χ^2=2.75 (0.43)
rs1360780 (CC/T*)	13/16	16/15	9/12	10/15	χ^2=0.83 (0.84)
FKBP5 methylation	60.74 ± 3.36	62.11 ± 3.69	59.36 ± 3.77	60.75 ± 4.89	F=2.06 (0.11)
HAMD	2 (0-7)	29 (17-45)	0 (0-5)	23 (6-31)	KW=84.11 (<0.01)
BDI	1 (0-12)	31 (5-59)	1 (0-13)	34 (17-51)	KW=69.08 (<0.01)
CTQ	30 (25-48)	40 (25-88)	28 (25-53)	36 (25-82)	KW=21.28 (<0.01)
Medication		9/12/7/3		4/14/5/2	χ^2=2.00 (0.74)
Illness duration (years)		14 (0.70-14.40)		4.42 (0-56)	U=5.62 (0.02)

Table 16 – Demographic and questionnaire scores. For parametric variables, mean and standard deviation are given. For non-parametric variables, the median as well as minimum and maximum values are given. Medication is expressed as none/SSRI/SNRI/other (antipsychotic or agomelatine) CTQ=childhood trauma questionnaire; HAMD=Hamilton rating scale for depression, BDI=Beck depression inventory; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors.

13.3.2 *Behavioural analysis*

Concerning the number of hits, we detected an interaction between diagnosis, trial type and valence (Wald χ^2=10.11, p<0.01). Analysing individual trials, patients showed less hits especially in neutral and positive ERT (Table 17).

We detected a significant interaction between diagnosis and trial type in predicting response times (Wald χ^2=5.17, p=0.02). Post-hoc testing revealed that MDD were overall slower in responding to SRT (Wald χ^2=4.87, p=0.03). This effect was especially present in negative and positive SRT (Wald χ^2=5.09, p=0.02, Table 17).

Allele rs1360780 did not show any effect on number of hits or response times.

Effect	HC	MDD	Wald χ^2 (p)
Hits ERT Neu	22.51 ± 4.32	23.80 ± 3.96	3.97 (0.046)
Hits ERT Neg	25.83 ± 4.20	24.14 ± 5.87	2.49 (0.11)
Hits ERT Pos	24.70 ± 4.75	22.42 ± 5.91	5.49 (0.02)
Hits SRT Neu	26.36 ± 4.40	24.34 ± 5.98	3.41 (0.06)
Hits SRT Neg	25.26 ± 3.98	24.16 ± 4.95	1.21 (0.27)
Hits SRT Pos	25.45 ± 4.21	24.52 ± 5.04	0.79 (0.37)
RT ERT Neu (s)	1.38 ± 0.33	1.46 ± 0.34	0.48 (0.49)
RT ERT Neg (s)	1.24 ± 0.33	1.33 ± 0.32	0.98 (0.34)
RT ERT Pos (s)	1.20 ± 0.28	1.27 ± 0.27	0.52 (0.47)
RT SRT Neu (s)	1.25 ± 0.30	1.37 ± 0.30	2.60 (0.12)
RT SRT Neg (s)	1.23 ± 0.34	1.40 ± 0.36	5.09 (0.02)
RT SRT Pos (s)	1.26 ± 0.29	1.40 ± 0.28	3.78 (0.05)

Table 17 – Task performance. Hits and incorrect responses are given as counts, reaction times (RT) are given as mean±standard deviation. HC=healthy controls; MDD=depressed patients; ERT=emotional recognition trials; SRT=shape recognition trials; Neu=neutral; Neg=negative; Pos=positive.

13.3.3 *Predictors of FKBP5 methylation*

Our GLM analysis (see Table 18 for model information) returned a significant effect for the triple interaction between diagnosis, rs1360780 and CTQ (F=4.06, p=0.047). Post-hoc testing revealed a significant role for higher CTQ in predicting lower mean FKBP5 intron methylation in the T* MDD group (F=4.95, p=0.036, Figure 17). In the GLM, a significant interaction between diagnosis and rs1360780 was also detected (F=5.05, p=0.03). Post-hoc testing showed a higher mean FKBP5 in-

tron methylation in patients among participants carrying the T allele (F=4.35, p=0.042).

Effect	F-test (p)
Diagnosis	2.53 (0.13)
Site	3.21 (0.06)
Sex	17.99 (<0.01)
rs1360780	0.19 (0.65)
Age	0.87 (0.40)
CTQ	0.46 (0.51)
Diagnosis*rs1360780	5.05 (0.03)
rs1360780*CTQ	0.77 (0.38)
Diagnosis*CTQ	1.40 (0.23)
Diagnosis*rs1360780*CTQ	4.16 (0.047)

Table 18 – Results for our general linear model predicting mean peripheral FKBP5 intron 7 methylation across all participants. A significant interaction between diagnosis, rs1360780 allele status and CTQ was found (F=4.16, p=0.047). CTQ=childhood trauma questionnaire.

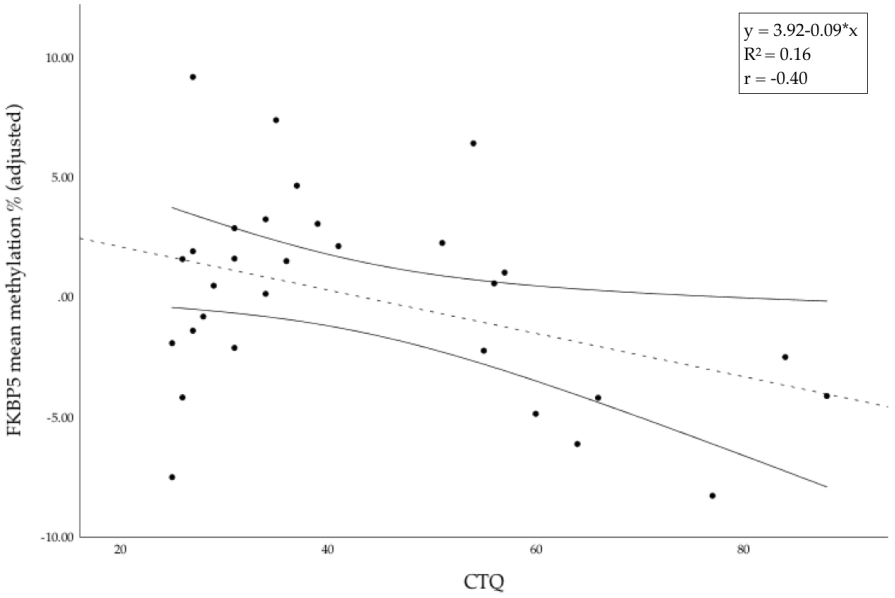

Figure 17 – Correlation between peripheral mean *FKBP5* methylation in T* patients and CTQ scores. Lower peripheral DNA methylation of *FKBP5* intron 7 was associated to a higher exposure to childhood adversity in patients carrying the T allele of rs1360780 (F=4.95, p=0.04). Methylation values are adjusted for age, sex, sex, site and medication (residuals) and a least-squares fit line is shown along with the 95% confidence interval of the mean. Fit, effect size and slope of the correlation are given in the legend. CTQ=childhood trauma questionnaire.

13.3.4 *Effect of FKBP5 methylation on brain structure and function*

Our GEE models investigating the role of mean FKBP5 intron methylation in predicting gray matter concentration (see Table 19 for models summary) returned a significant main effect for the IFGO across all participants (Wald chi-square=11.93, p_{FDR}<0.01, Figure 18).

Region	Effect	Wald χ^2 (p_{FDR})
AMY	Diagnosis	0.01 (0.98)
	rs1360780	1.27 (0.56)
	FKBP5 methylation	0.35 (0.74)
	Diagnosis*rs1360780	0.62 (0.71)
	Diagnosis*FKBP5 methylation	0 (0.98)
	rs1360780*FKBP5 methylation	1.23 (0.58)
	Diagnosis*rs1360780*FKBP5 methylation	0.66 (0.71)
ACC	Diagnosis	0.79 (0.71)
	rs1360780	0.03 (0.93)
	FKBP5 methylation	0.03 (0.94)
	Diagnosis*rs1360780	2.85 (0.24)
	Diagnosis*FKBP5 methylation	0.63 (0.71)
	rs1360780*FKBP5 methylation	0.04 (0.93)
	Diagnosis*rs1360780*FKBP5 methylation	2.76 (0.26)
HIP	Diagnosis	0.18 (0.79)
	rs1360780	1.62 (0.47)
	FKBP5 methylation	0.97 (0.64)
	Diagnosis*rs1360780	0.65 (0.71)
	Diagnosis*FKBP5 methylation	0.13 (0.84)
	rs1360780*FKBP5 methylation	1.82 (0.43)
	Diagnosis*rs1360780*FKBP5 methylation	0.66 (0.71)
IFG	Diagnosis	1.52 (0.50)
	rs1360780	0.29 (0.76)
	FKBP5 methylation	1.4 (0.53)
	Diagnosis*rs1360780	0.56 (0.71)
	Diagnosis*FKBP5 methylation	1.41 (0.53)
	rs1360780*FKBP5 methylation	0.23 (0.77)

Region	Effect	Wald χ^2 (p_{FDR})
	Diagnosis*rs1360780*FKBP5 methylation	0.76 (0.71)
IFO	Diagnosis	0.56 (0.71)
	rs1360780	0.2 (0.78)
	FKBP5 methylation	3.69 (0.17)
	Diagnosis*rs1360780	0.00 (0.98)
	Diagnosis*FKBP5 methylation	0.71 (0.71)
	rs1360780*FKBP5 methylation	0.28 (0.76)
	Diagnosis*rs1360780*FKBP5 methylation	0.00 (0.98)
IFGO	Diagnosis	0.24 (0.77)
	rs1360780	0.51 (0.71)
	FKBP5 methylation	11.93 (<0.01)*
	Diagnosis*rs1360780	0.28 (0.76)
	Diagnosis*FKBP5 methylation	0.36 (0.74)
	rs1360780*FKBP5 methylation	0.59 (0.71)
	Diagnosis*rs1360780*FKBP5 methylation	0.23 (0.77)
INS	Diagnosis	0.53 (0.71)
	rs1360780	0.01 (0.97)
	FKBP5 methylation	2.67 (0.26)
	Diagnosis*rs1360780	0.52 (0.71)
	Diagnosis*FKBP5 methylation	0.53 (0.71)
	rs1360780*FKBP5 methylation	0.02 (0.96)
	Diagnosis*rs1360780*FKBP5 methylation	0.57 (0.71)
MFO	Diagnosis	4.47 (0.12)
	rs1360780	0.58 (0.71)
	FKBP5 methylation	4.55 (0.10)
	Diagnosis*rs1360780	0.13 (0.84)
	Diagnosis*FKBP5 methylation	4.74 (0.10)
	rs1360780*FKBP5 methylation	0.75 (0.71)
	Diagnosis*rs1360780*FKBP5 methylation	0.24 (0.77)
MFG	Diagnosis	0.35 (0.75)
	rs1360780	0.73 (0.71)
	FKBP5 methylation	0.01 (0.98)
	Diagnosis*rs1360780	1.04 (0.63)

Region	Effect	Wald χ^2 (p_{FDR})
	Diagnosis*FKBP5 methylation	0.3 (0.76)
	rs1360780*FKBP5 methylation	0.82 (0.70)
	Diagnosis*rs1360780*FKBP5 methylation	1.1 (0.61)
MFOG	Diagnosis	0.01 (0.98)
	rs1360780	0.6 (0.71)
	FKBP5 methylation	2.28 (0.33)
	Diagnosis*rs1360780	0.98 (0.63)
	Diagnosis*FKBP5 methylation	0.03 (0.94)
	rs1360780*FKBP5 methylation	0.61 (0.71)
	Diagnosis*rs1360780*FKBP5 methylation	1.09 (0.62)
SFG	Diagnosis	0.52 (0.71)
	rs1360780	0.00 (1.00)
	FKBP5 methylation	0.22 (0.77)
	Diagnosis*rs1360780	0.25 (0.77)
	Diagnosis*FKBP5 methylation	0.47 (0.72)
	rs1360780*FKBP5 methylation	0 (0.98)
	Diagnosis*rs1360780*FKBP5 methylation	0.28 (0.76)
SFO	Diagnosis	0.37 (0.74)
	rs1360780	0.09 (0.88)
	FKBP5 methylation	3.03 (0.22)
	Diagnosis*rs1360780	1.93 (0.41)
	Diagnosis*FKBP5 methylation	0.33 (0.75)
	rs1360780*FKBP5 methylation	0.09 (0.88)
	Diagnosis*rs1360780*FKBP5 methylation	1.73 (0.45)
SMF	Diagnosis	0.38 (0.74)
	rs1360780	0.39 (0.74)
	FKBP5 methylation	0.42 (0.74)
	Diagnosis*rs1360780	0.05 (0.91)
	Diagnosis*FKBP5 methylation	0.43 (0.74)
	rs1360780*FKBP5 methylation	0.42 (0.74)
	Diagnosis*rs1360780*FKBP5 methylation	0.06 (0.91)

Region	Effect	Wald χ^2 (p_{FDR})

Table 19 – Effects of interest for our models predicting gray matter concentration across all participants. We detected a significant negative prediction (*) of mean FKBP5 intron methylation in the IFGO (Wald chi-square=11.41, p_{FDR}<0.01). Main effects of site, sex, age, total intracranial volume, side were included in the models but are not shown for brevity. For region abbreviations, see Table 15; IFGO=inferior frontal gyrus pars orbitalis.

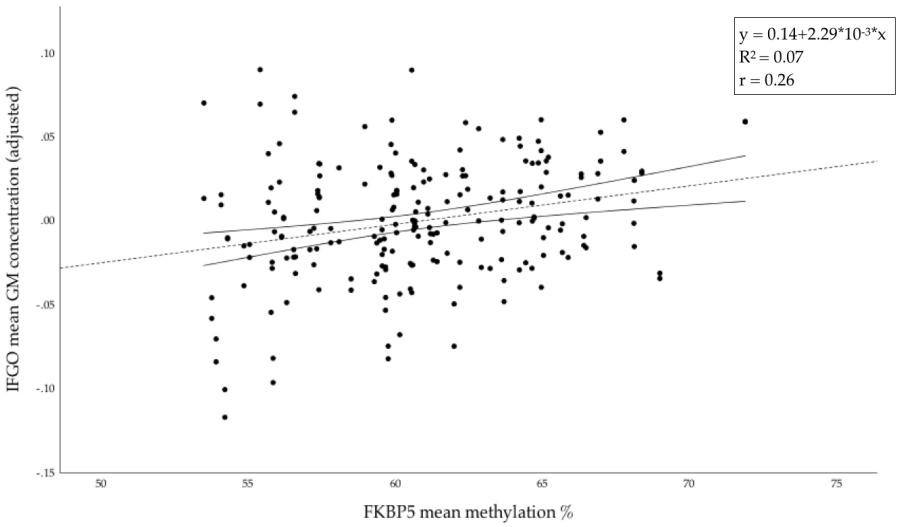

Figure 18 – Correlation between IFGO mean GM concentration and peripheral mean FKBP5 methylation across all participants. Lower peripheral DNA methylation of *FKBP5* intron 7 was associated to a lower mean GM concentration (Wald chi-square=11.9341, p_{FDR}<0.01, to account for 13 regions). GM values are adjusted for site, age, TIV, diagnosis, sex, medication, rs1360780 and side (residuals) and a least-squares fit line is shown along with the 95% confidence interval of the mean. Fit, effect size and slope of the correlation are given in the legend. IFGO=inferior frontal gyrus pars orbitalis; GM=gray matter.

All ROIs were significantly activated in the ERT>SRT contrast across all participants across all valences (all p<0.001), with the exception of the inferior frontal gyrus pars opercularis (t=-0.25, p=0.80), insula (t=0.36, p=0.72), middle frontal gyrus pars orbitalis (t=-1.70, p=0.09) and superior frontal gyrus pars orbitalis (t=-0.93, p=0.35), which were therefore excluded from the functional analysis.

In the IFGO, we found a significant interaction between diagnosis and FKBP5 intron methylation in predicting functional responses (Wald chi-square=6.57, p_{FDR}=0.049, see Table 20 for models summary).

Region	Effect	Wald χ^2 (p_{FDR})
AMY	Diagnosis	0.51 (0.67)
	rs1360780	0.01 (0.94)
	FKBP5 methylation	1.5 (0.50)
	Diagnosis*rs1360780	2.02 (0.41)
	Diagnosis*FKBP5 methylation	0.45 (0.68)
	rs1360780*FKBP5 methylation	0.03 (0.92)
	Diagnosis*rs1360780*FKBP5 methylation	2.20 (0.40)
ACC	Diagnosis	0.54 (0.67)
	rs1360780	0.60 (0.67)
	FKBP5 methylation	0.35 (0.71)
	Diagnosis*rs1360780	0.6 (0.67)
	Diagnosis*FKBP5 methylation	0.33 (0.72)
	rs1360780*FKBP5 methylation	0.94 (0.63)
	Diagnosis*rs1360780*FKBP5 methylation	0.73 (0.67)
HIP	Diagnosis	0.03 (0.93)
	rs1360780	0.26 (0.75)
	FKBP5 methylation	1.14 (0.57)
	Diagnosis*rs1360780	0.41 (0.68)
	Diagnosis*FKBP5 methylation	0.03 (0.92)
	rs1360780*FKBP5 methylation	0.41 (0.68)
	Diagnosis*rs1360780*FKBP5 methylation	0.53 (0.67)
IFG	Diagnosis	1.12 (0.57)
	rs1360780	4.7 (0.13)
	FKBP5 methylation	0.52 (0.67)
	Diagnosis*rs1360780	0.74 (0.67)
	Diagnosis*FKBP5 methylation	1.14 (0.57)
	rs1360780*FKBP5 methylation	5.09 (0.09)
	Diagnosis*rs1360780*FKBP5 methylation	0.78 (0.67)
IFGO	Diagnosis	6.13 (0.05)
	rs1360780	0.22 (0.78)
	FKBP5 methylation	0.63 (0.67)
	Diagnosis*rs1360780	0.69 (0.67)
	Diagnosis*FKBP5 methylation	6.57 (0.049)*

Region	Effect	Wald χ^2 (p_{FDR})
	rs1360780*FKBP5 methylation	0.12 (0.84)
	Diagnosis*rs1360780*FKBP5 methylation	0.67 (0.67)
MFO	Diagnosis	1.76 (0.42)
	rs1360780	0.52 (0.67)
	FKBP5 methylation	2.19 (0.40)
	Diagnosis*rs1360780	0.01 (0.94)
	Diagnosis*FKBP5 methylation	1.94 (0.41)
	rs1360780*FKBP5 methylation	0.44 (0.68)
	Diagnosis*rs1360780*FKBP5 methylation	0.01 (0.95)
MFG	Diagnosis	0.6 (0.67)
	rs1360780	3.58 (0.22)
	FKBP5 methylation	0.05 (0.91)
	Diagnosis*rs1360780	0.16 (0.81)
	Diagnosis*FKBP5 methylation	0.49 (0.67)
	rs1360780*FKBP5 methylation	3.05 (0.27)
	Diagnosis*rs1360780*FKBP5 methylation	0.15 (0.81)
SFG	Diagnosis	1.25 (0.57)
	rs1360780	1.88 (0.41)
	FKBP5 methylation	0.85 (0.66)
	Diagnosis*rs1360780	0.04 (0.92)
	Diagnosis*FKBP5 methylation	1.07 (0.58)
	rs1360780*FKBP5 methylation	2.00 (0.41)
	Diagnosis*rs1360780*FKBP5 methylation	0.04 (0.92)
SMF	Diagnosis	1.99 (0.41)
	rs1360780	4.06 (0.15)
	FKBP5 methylation	0.63 (0.67)
	Diagnosis*rs1360780	0.53 (0.67)
	Diagnosis*FKBP5 methylation	1.91 (0.41)
	rs1360780*FKBP5 methylation	4.64 (0.13)
	Diagnosis*rs1360780*FKBP5 methylation	0.63 (0.67)

Region	Effect	Wald χ^2 (p_{FDR})

Table 20 – Results for our models predicting activation for ERT>SRT across all participants. We detected a significant interaction (*) between mean FKBP5 intron methylation and diagnosis in the IFGO (Wald χ^2==6.57, p_{FDR}=0.049). Main effects of site, sex, age, valence, side were included in the models but are not shown for brevity. For region abbreviations, see Table 15; IFGO=inferior frontal gyrus pars orbitalis.

Post-hoc investigation revealed that FKBP5 intron methylation showed a negative correlation with activation only in MDD regardless of valence and side (see Table 21 for model summary, Wald chi-square=5.58, p=0.02, Figure 19).

Effect	Wald χ^2 (p)
Site	16.68 (<0.01)
Sex	0.31 (0.58)
Medicated	3.40 (0.07)
Age	6.78 (0.01)
Side	16.53 (<0.01)
rs1360780	1.65 (0.20)
Valence	0.88 (0.64)
FKBP5 methylation	5.58 (0.02)
rs1360780*FKBP5 methylation	1.71 (0.19)

Table 21 – Results for our generalized estimating equation models predicting mean activation for ERT>SRT in MDD patients in the IFGO. We detected a significant negative prediction of mean FKBP5 intron methylation (Wald chi-square=5.58, p=0.02). IFGO=inferior frontal gyrus pars orbitalis; df=degrees of freedom; ERT=emotion recognition trials; SRT=shape recognition trials.

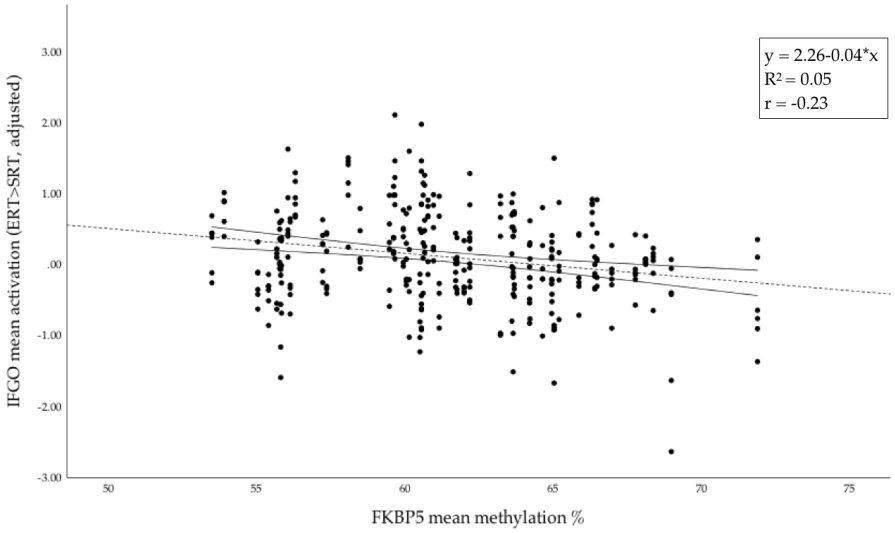

Figure 19 – Correlation between IFGO mean activation and peripheral mean *FKBP5* methylation in MDD. Lower peripheral DNA methylation of *FKBP5* intron 7 was associated to a lower activation in ERT>SRT in patients carrying the T allele of rs1360780 (Wald χ^2==5.58, p=0.02). Activation values are adjusted for site, age, TIV, sex, medication, rs1360780, valence and side (residuals) and a least-squares fit line is shown along with the 95% confidence interval of the mean. Fit, effect size and slope of the correlation are given in the legend. IFGO=inferior frontal gyrus pars orbitalis, ERT=emotional recognition trials, SRT=shape recognition trials.

GM concentration in the IFGO was not different between MDD and HC (Wald chi-square=0.37, p_{FDR}=0.76). However, its activation was lower in MDD compared to HC regardless of valence, age, side and rs1360780 allele status (Wald chi-square=3.88, p_{FDR}=0.049). Its activation was also significantly negatively correlated with BDI in MDD (Wald chi-square=4.65, p=0.03).

13.4 DISCUSSION

Firstly, our study supports the hypothesis that, in the subpopulation of MDD patients carrying the high-risk T allele of rs1360780, methylation of *FKBP5* introns is higher and correlated to exposure to chronic stress in early life. This finding is present in numerous studies, both preclinical (Klengel et al., 2013) and clinical ones ranging across several chronic stress conditions (Tyrka, Ridout, and Parade, 2016; Provencal and Binder, 2015; Resmini et al., 2016; Tyrka et al., 2015; Klengel et al., 2013). We therefore expand to patients showing depressive symptoms the notion that *FKBP5* demethylation is a correlate of exposure to childhood adversity, highlighting the role of rs1360780 as a moderator of this effect.

Furthermore, across all participants, lower *FKBP5* intron methylation levels were associated with reduced grey matter concentration in the inferior frontal orbital gyrus. This region has been associated with response inhibition in general (Aron, Robbins, and Poldrack, 2004; Chikazoe et al., 2007) and, in particular, reappraisal and modulation of negative emotion (Goldin et al., 2008; Blair et al., 2007). Overall, several studies hint at structural changes in the orbitofrontal cortex in MDD (Phillips et al., 2003b; Sexton, Mackay, and Ebmeier, 2013; Bremner et al., 2002; Lacerda et al., 2004; Drevets, 2007), a finding that was confirmed at a meta-analytical level (Kempton et al., 2011). In a recent study comparing youths with post-traumatic stress disorder and controls, a negative association between grey matter in this region and evening cortisol levels across all participants was shown, regardless of diagnosis (Carrion et al., 2010). Though causality could not be tested yet, our results suggest that *FKBP5* methylation might be related to GR function in chronic stress conditions regardless of diagnosis and might influence the structural integrity of the inferior frontal orbital gyrus, similar to what has been observed in the prefrontal cortex of rats (Guidotti et al., 2013). Since cortisol measures were not available and childhood adversity was considerably more present in our depressed patients, we can provide supporting evidence for this theory only in our MDD T* group, in which *FKBP5* intron demethylation was specifically explained by exposure to childhood adversity.

We found activation of the IFGO to be reduced in MDD patients compared to HC, and to be inversely correlated with the self-reported intensity of symptoms. Interestingly, in this group, *FKBP5* methylation was negatively correlated with IFGO hemodynamic response during our emotional recognition task. This finding is surprising, since after observing that lower *FKBP5* methylation was associated with lower GM in the IFGO, we expected it would rather mirror a reduction of function in this region. Considering the relationship between *FKBP5* methylation and chronic stress exposure, these results might be interpretable in light of the increased activation in the inferior frontal gyrus during emotion classification in hypercortisolemic patients (Langenecker et al., 2012). Also, given that patients with higher activity reported lower symptoms, this finding could suggest that chronic stress exposure might lead to increased resilience and higher compensatory functional responses to emotional content in some individuals (Feder, Nestler, and Charney, 2009). On the other hand, HPAA dysregulation has been associated with more severe depressive

symptoms intensity in the past (Burke et al., 2005; Pruessner et al., n.d.; Guidotti et al., 2013). Since the effect of medication approached significance in predicting higher activity in the IFGO ($p=0.07$), another possibility might be that *FKBP5* epigenetics could play a role in successful response to antidepressant therapy, although methylation was not different between treated and untreated patients in our sample, nor in (Han et al., 2017).

This study is not without limitations. First of all, it is necessary to address the fact that most of our patients were medicated and, although we corrected for medication use in all of our models, we cannot exclude that our results might be confounded by this factor. Secondly, our results differ from those reported by Han et al., 2017 in a recent similar study. This might be due to several reasons, such as the use of different methods (VBM and fMRI compared to automated cortical segmentation using Freesurfer) and a different choice of ROIs and statistics. However, the present study addresses some of the limitations highlighted in Han et al., 2017 , for example the investigation of the role of childhood trauma in predicting *FKBP5* intron methylation, which we consider valuable for the interpretation of our findings. Furthermore, both studies are in agreement in highlighting the inferior frontal gyrus as a crucial site for the role of FKBP5 on brain structure. Also, we did not have reliable measures of HPAA function, such as cortisol levels. Another important point to be addressed is the still not well-known association between peripheral and central *FKBP5* methylation. Some recent studies show some convergence between FKBP5 methylation derived from peripheral blood and brain tissue from certain regions, such as the hippocampus (Ewald et al., 2014) but others have highlighted the applicability of these findings only to some genes and portions of the brain (Hannon et al., 2015). The results of the present study suggest that peripheral *FKBP5* methylation might be linked to brain structure and function, but experimental research on this link is necessary. The mechanisms involved could be complex, ranging from differences between regions in brain maturation as well as their sensibility to glucocorticoid action. More preclinical studies are surely needed to understand which regions show local epigenetic changes that are related to peripheral ones. This would allow clinical research to focus on measurable markers reflecting functional modifications in specific molecular pathways within the brain. Overall, future studies might also overall benefit from the investigation of the interaction between known genetic variants of FKBP5 and

its methylation in large cohorts of medicated and unmedicated MDD patients, carefully controlling for childhood trauma levels, directly assessing HPAA axis function and focusing on imaging the inferior frontal gyrus.

13.5 CONCLUSION

To summarize, in a subgroup of MDD patients carrying the high-risk allele of the *FKBP5* rs1360780 SNP, exposure to childhood trauma was inversely correlated to peripheral DNA methylation percentage of this gene. Across all participants, lower FKBP5 methylation was associated with decreased grey matter in the inferior frontal orbital gyrus. In the MDD group, it also negatively correlated with its activation. This region is linked with emotional regulation and was functionally hypoactive in MDD in our sample, with its activation being negatively correlated with self-reported symptoms severity. Our findings suggest that epigenetic changes of *FKBP5* might be a link connecting the interaction of genetic and environmental risks with brain changes in an area relevant for the clinical symptoms of depression.

Part IV

DISCUSSION

14

DISCUSSION

Given the results from our experiments reported in Chapters 11, 12 and 13, we can now provide a comprehensive description of the interaction between a high-risk SNP of the *FKBP5* gene, its epigenetic changes, chronic environmental stress in the form of childhood maltreatment and functional as well as structural brain changes in emotional processing areas in MDD.

Our results will be summarized to provide an overview of the demographic, clinical, behavioural and imaging findings emerged from our studies. Then, for each aspect, an overall interpretation will be provided, limitations will be highlighted and future directions will be suggested.

14.1 SAMPLE CHARACTERISTICS

Overall, we were successful in recruiting a sufficient number of participants to investigate our effects of interest. Concerning some of the demographic variables we collected, however, some limitations of our recruitment procedure need to be addressed.

First of all, when considering our complete dataset, the mean age of MDD was higher than the one of HC. We were able to select subsets of our data for the individual experiments to eliminate this discrepancy and corrected statistically for the effect of age in all of our analyses. However, given that our patients were spread across a wide range of ages, from the early twenties to the early sixties, we still cannot exclude that age might be a confound in our findings. In particular, structural brain properties, such as gray matter or diffusion measures, show a decline with age. In our study on rs1360780, patients carrying the T allele of the SNP were significantly older than CC ones, suggesting that our results might have been confounded by this factor.

Also, three controls from the TCIN sample were related (sister and cousin), which might have added a confound for our genetical and morphological analyses. Since genotyping of *FKBP5* in our sample reflected results known from the general population, we think that

this mistake in the recruitment procedure could have played only a small role.

We also encountered difficulties in matching our groups in regards to some lifestyle variables, such as BMI, which was higher in MDD in both of our datasets. This could be due to the comorbidity of MDD with chronic metabolic conditions such as diabetes (Scott et al., 2007) but also to the complex associations of BMI with wider environmental factors such as lower socio-economical status, stress and poorer education, which are all risk-factors for MDD (Brown, Harris, and Hepworth, 1994; Lorant et al., 2007). The causes for these differences would be hard to disentangle but it is worth noting that the average BMI for our groups was maintained between the higher portion of the normal range and the lower one of the overweight range. Since the participants were not affected by clinically relevant obesity, we believe this could play only a neglectable role in our findings.

Another noteworthy confound was the significantly higher education level of controls compared to patients. Lower socio-economic status is a known risk-factor for MDD (Brown, Harris, and Hepworth, 1994; Lorant et al., 2007) and this is why a difference in this variable between our grous could have been expected. Still, education impacts on brain structure (Noble et al., 2015) and this discrepancy could represent a major confound in our findings.

Compatibly with epidemiological data, the number of females outweighed the one of males in our MDD participants (Alonso et al., 2004; Blazer et al., 1994; Kessler et al., 2003; Patten et al., 2006). In our experiments, it did so both in the MDD and in the HC groups, therefore making the effects of sex possible to assess and remove statistically as a confound variable. Given the comparatively low number of males, however, it was not possible to investigate the interaction of sex with variables of interest. In particular, it has been shown that sex is a relevant moderator of the effects of childhood adversity in MDD on brain structure (Frodl et al., 2016).

Concerning smoker and partnership status, these variables were different between groups only in respectively the TCIN and CAMI dataset, possibly because the first featured older participants than the second. Even if these effects were limited, it is still worth noting that smoking in particular is known to be associated with chronic inflammation (Lee, Taneja, and Vassallo, 2012). Considering the postulated importance of inflammation in the pathogenesis of MDD and

its interconnection with stress (see Chapter 1), this confound should be taken into consideration at least regarding some of our studies.

Clinically, our MDD participants were well characterized by the classically described constellation of symptoms, featuring anhedonia, low mood, changes in appetite, sleep disturbances and somatic manifestations of anxiety (see Chapter 1). Two major confounds need to be addressed regarding clinical variables in our datasets. The first is the almost complete absence of HC having been exposed to childhood adversity, which made it impossible for us to investigate it in the absence of MDD. The use of CTQ total score as a linear variable helped us in disentangling the effects of adversity and diagnosis, since a binary factor for childhood maltreatment would have shown marked collinearity with the latter. Still, our results concerning this effect could not be extended to HC and could in part mask or be masked by those of MDD. Also, CTQ suffers from the limitation of being a self-rated retrospective scale, therefore we cannot exclude that the subjectivity of answers might have biased our findings. Secondly, the vast majority of our MDD patients was treated, which is not surprising since our main site of recruitment was the outpatients clinic of a hospital (see Chapter 7). Even though we modelled medication as a confound in all of our investigations within the MDD cohort, this is a major confound that needs to be highlighted, since psychiatric medication is known to affect brain structure and function (Dusi et al., 2015; Wessa and Lois, 2015).

14.2 BEHAVIOURAL FINDINGS

During the execution of our emotion recognition task, in two out of our three studies MDD performed worse across all trials. Differences in specific trials were discordant between our first two studies and the third one, which featured a merged dataset across the two sites. The three studies, however, agreed in highlighting a lower number of hits in the positive ERT condition, which might be a correlate of the inability of depressed subjects to correctly identify positive stimuli as such (Murrough et al., 2011; Bylsma, Morris, and Rottenberg, 2008). It is worth noting that MDD task performance was consistently but only slightly lower than the one of HC, with an average difference oscillating around 2 hits.

The analysis of response times gave conflicting results, with patients being as fast as controls in the first study, being overall slower in

the second and being slower only in certain trials in the third. Given the differences in the demographic composition between the CAMI and TCIN datasets, we believe age might play a role in these findings. This factor was a strong predictor of response times in all samples and it is possible that it might interact with diagnosis to give an overall poorer performance in older MDD. With our current data, however, it is hard to draw a definitive conclusion about the way MDD affects response times in our task.

Interestingly, in our gPPI study, better task performance in patients correlated with a higher connectivity within the task-positive network. Given the relatively low number of errors in the task across all participants, however, it is hard for us to make in-depth considerations about whether the fMRI correlates of our task might be predictive of performance. To do so, harder tasks with more trials are probably needed, which might necessitate the engagement of more cognitive processes which are known to be impaired in depression such as attention.

14.3 fMRI of emotional regulation in MDD

Our fMRI task showed a pattern of activation compatible with our hypotheses concerning the areas involved in emotional processing. Namely, emotion recognition was associated with the activation of the medial and inferior portions of the frontal lobe as well as of the amygdala, insula, hippocampus and temporal lobes. On the other hand, while participants directed their attention away from the emotional content of the stimuli, dorsolateral prefrontal and parietal areas were more active.

Concerning differences in activation between MDD and HC, they involved a lower activation across all task conditions in the hippocampus, middle frontal gyrus and precuneus as well as a lower one of the insula and inferior frontal gyrus pars orbitalis during ERT compared to SRT. As previously shown in comparable tasks, recognition and regulation of emotion are well suited to highlight fMRI differences between MDD patients and HC. Therefore, these results were not entirely surprising, since these regions have been shown to be affected in MDD patients across numerous studies (see Chapter 4 for an overview). Findings, however, were not always consistent across our datasets. There are several possible reasons for this, the main one being differences in head coils and sequences between the two scanning

sites. Also, depending on the objectives of our studies, we performed analyses aimed at assessing different effects of interest in each experiment, which were therefore different from one another. In the future, our datasets might prove valuable resources for replication studies by conducting identical analyses on data featuring the same task run at two different scanning sites.

In our gPPI study, we also highlight how, during emotional recognition, activated regions increase their functional connectivity with each other and with areas involved in emotion regulation. While performing our task, MDD patients showed altered connectivity patterns between several of these regions, particularly in trials involving the voluntary attentional regulation of negative pictures or the emotional recognition of positive ones. The amygdala and ACC were specially involved, along with regions belonging to the task-positive and default mode networks. Our analysis was exploratory in nature, since functional connectivity during emotion processing had not yet been extensively investigated in MDD. Future studies should therefore target these regions and networks selectively, to analyse in depth how their function relates to the clinical symptoms of MDD.

To sum up, MDD patients showed differences in activation in regions involved in emotional recognition. Functional connectivity between some of these regions and between areas belonging to the task-positive and default mode networks was also altered, in particular in trials involving regulation of negative emotions and recognition of positive ones.

14.4 FBKBP5 IN MDD

The high-risk T allele of the rs1360780 SNP was not more represented in the MDD population as in the HC in our samples. This might be due to the fact that our sample was much smaller than the one used for genetic linkage studies and that we had to pool T homozygous and heterozygous participants to achieve a sufficient group size.

The first role of this polymorphism to emerge from our data was that it associated with structural and functional changes in areas involved in emotion processing, both in MDD and HC. In particular, across both groups, T* allele status participants showed lower responses in several such regions, such as the middle, inferior frontal and orbitofrontal gyri, insula, hippocampus and posterior cingulate

cortex. Furthermore, T* MDD patients featured specific differences in activation compared to their CC counterparts in the insula, rolandic operculum and inferior frontal gyrus. These functional changes were also mirrored by structural differences as assessed by diffusion imaging. Our results, therefore, lead us to postulate a role of genetic variants of *FKBP5* in influencing structure and function of these regions.

A second crucial role of rs1360780 that emerges from our studies is as a mediator of the effects of prolonged stress exposure in childhood. In particular, we have shown that in patients carrying its high-risk allele, demethylation of the intron sites of the *FKBP5* gene promoter was correlated with the amount of early life maltreatment endured. Therefore we suggest, compatibly with other preclinical and clinical studies (see Chapter 13 for details), that the presence of both genetic and environmental risk factors is able to produce lasting epigenetic changes in a gene that has a prominent role in GR regulation. In our data, this could be observed only in patients with MDD, possibly because of the much greater amount of childhood maltreatment they had endured.

Even though with the present dataset we cannot draw any causal link, since our data is cross-sectional, we bring evidence suggesting that this interaction might impact structure and function of brain areas involved in emotional regulation. First of all, childhood maltreatment explained the decreased FA in our T* compared to our CC MDD in the rolandic operculum. It should be noted, however, that the differences in diffusion measures we have detected were small or small to moderate in effect size and that it is unclear how low levels of FA might be related to grey matter microstructure. Across our studies, we have also highlighted the role of the inferior frontal lobe as a region which is influenced by *FKBP5* allelic status and methylation, in line with the only other existing study on the topic (Han et al., 2017). This area was less active in MDD carrying the T allele of rs1360780 and in it demethylation of *FKBP5* was associated with lower grey matter concentration in both MDD and HC. Crucially, the inferior frontal gyrus was less active during emotional recognition in MDD compared to HC and its activation was inversely correlated with depression severity. Surprisingly, we found demethylation of *FKBP5* to be correlated to a higher activation of this region in MDD, suggesting that chronic stress exposure might lead to higher compensatory functional responses to emotional content in some individuals. Following up on our results, future studies should investigate this region

specifically and carefully correct for potential confounds effects on its activation such as those of antidepressant treatment.

It is worth noting that we could not assess whether the effects we detected were mediated by glucocorticoid hormones directly, since we did not record measures of GR sensitivity such as cortisol secretion in response to the administration of dexamethasone. Therefore, we have to rely on previous clinical and preclinical findings to postulate that the effects of GR dysregulation might be the potential causes of the link between *FKBP5* and the neuroimaging changes we have described.

14.5 FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

To sum up, even if the numerosity, demographic and clinical characteristics of the dataset were suitable to conduct our studies, future investigations should further attempt to remove the influence of lifestyle confounds, such as smoking, differences in education and BMI. Furthermore, to investigate complex interactions involving sex, the male MDD population should be target specifically. Also, studies assessing the role of childhood trauma should give a high priority to finding individuals exposed to this risk factor who never developed a psychiatric illness, even if it arguably constitutes a challenging task. Finally, effort should be invested in setting up recruitment pipelines targeted at first presentation patients specifically, in order to eliminate the effects of long term psychopharmacological treatment on brain imaging.

The effects we have shown range from small to moderate size, which is not uncommon among studies investigating genetic determinant of depression, which are often inconsistent (Dunn et al., 2015; Cohen-Woods, Craig, and McGuffin, 2013). In this regard, the task of reaching a sufficient sample size in such studies to investigate a gene by environment interaction on a whole-genome level has been highlighted as a major challenge for the years to come (Dunn et al., 2015). The targeting of specific genes and careful selection of participants based on known environmental risk-factors might be a way to obtain sufficient power to investigate such effects in the future, albeit blinding experimenters to potentially novel genetic findings in unexpected loci.

Genome-wide studies seeking SNPs associated with MDD had often negative and at best mixed results, possibly because of the key

importance of environmental factors in the disorder (see Dunn et al., 2015 for a review). Therefore, the genetic variants associated with MDD for which more evidence is available are still those obtained from smaller hypothesis-driven studies, which have targeted genes based on the current pathogenetic theories.

Also, behavioural performance in our emotional recognition task consistently highlighted a deficit of MDD participants in identifying the valence of positive stimuli. However, to investigate fMRI correlates of this deficit, future studies should consider tasks which are more challenging and feature a higher number of trials.

Given that we have highlighted the importance of functional connectivity between emotion-processing regions in MDD, future, investigations should focus on a smaller number of specific regions, to detect finer changes that might be related to the symptoms of the disorder. White matter tracts anatomically connecting them should also be more thouroughly investigated, using voxel-based approaches such as tract-based spatial statistics or targeted reconstruction. Anatomical neuronal inputs to the paraventricular nucleus of the hypothalamus, which is a core regulator of the HPAA, might also be investigated in detail using diffusion-weighted imaging.

Future studies should also work on linking the epigenetic and imaging changes we detected with measures of GR function, such as cortisol responses to the dexamethasone suppression test. Exposure to chronic stress in childhood should be investigated in the healthy population as well, to clarify which of our results are diagnosis specific and which are common to all maltreatment victims.

Finally, more preclinical studies are surely needed to understand which regions show local epigenetic changes that are related to peripheral ones. This would allow clinical research to focus on measurable markers reflecting functional modifications in specific molecular pathways within the brain.

Once enough evidence is collected, this research could give insight in the molecular mechanisms linking a prominent risk factor such as childhood adversity to depression. Furthermore, it might provide easily measurable biomarkers of this link in the form of non-invasive brain measurements and genetic as well as epigenetic characteristics that are easily quantifiable after collecting a peripheral blood sample. Being able to characterize this pathogenetic pathway routinely might enable clinicians to avail of targeted therapies and to identify the most appropriate treatment for each patient, speeding up their

recovery as well as reducing costs for the healthcare system. It might also affect policy development in the area of childhood trauma intervention, identifying victims who are more at risk of developing depression later in life as candidates for early intervention.

14.6 CONCLUSION

Taken together, findings across our three studies provide evidence that the gene coding for the glucocorticoid regulator *FKBP5* protein is a convergence point for the interplay between genetic and environmental risk factors of MDD. In particular, in individuals carrying its high-risk SNP, exposure to chronic stress in early life might lastingly modify the gene function through epigenetic mechanisms. This, in turn, could result in a deficit of GR responses and to structural as well as functional consequences on brain regions involved in emotional recognition and regulation as well as in the symptoms of MDD. Specifically, the inferior frontal gyrus is a likely prominent site for this interaction, although others might exist among the regions which were not included as ROIs in our investigations.

Part V

APPENDIX

a

ROLE OF THE APPLICANT

The applicant, together with Drs. Farrell and Doolin, recruited all the patients of the TCIN sample. To do this, he traveled to Tallaght Hospital and to the Mary Mercer Clinic in Jobstown weekly, where he sat in during clinical examinations of all patients showing depressive symptoms. After discussing their eligibility for the study with the consultant, he screened the patients throughly for MRI compatibility and inclusion criteria, collected their informed consent and gave them an appointment at Trinity College Campus. In the same way, the applicant also recruited controls by sending emails and printing leaflets with contact information for the study and screened their eligibility before giving them an appointment at TCIN.

After the participants arrived at TCIN, the applicant greeted them, conducted the clinical interviews, rated the scales and took the blood samples used in the study. He then trained the participants for the MRI task, accompanied them to the scanner and was present for the whole duration of the scan. After the participant had left the building, the applicant entered all the data collected in the study database and archived the MRI data on the laboratory computer in a standardized fashion.

The applicant supervised the setup and parameters of the MRI sequences used in the study, regularly consulting with the responsible technician and lead physicist of the Institute. He also programmed the Neurobehavioural Systems Presentation task used during the fMRI acquisition.

Under the supervision of Prof. Frodl, the applicant autonomously planned and conducted all analyses on the MRI data as well as all the statistical computations presented in this work and in the related publications. The only analysis presented in this work not conducted by the applicant is the genotyping and methylation quantification of *FKBP5*, which were conducted by Dr. Farrell.

All text contained in the present work as well as in the publications that derived from it is also original work from the applicant along with its typesetting using LaTeX.

b

ACKNOWLEDGMENTS

Firstly, I wish to express my gratitude to my PhD supervisor Prof. Thomas Frodl for his mentoring throughout the past three years of my work. He has always guided my research with kindness, enthusiasm and rigour: for that I am thankful. For their support, I would also like to mention the other former members of his team: Friedrich Wetterling and Hazel McCarthy.

I also thank my co-supervisor Prof. Andrew Harkin for his precious advice during my time spent at Trinity College. His preclinical input was always illuminating and greatly helped in broadening my perception of depression research. Along with him, my deepest gratitude goes to his PhD student Jennifer David, with whom I worked closely within the framework of my research network and who has since grown to be one of my closest friends. From his research group, I would also like to thank Allison McIntosh for introducing me to the complex world of animal depression models.

I owe much to the members of the REDEEM team, guided by Prof. Veronica O'Keane, who kindly welcomed me in her clinic along with her own PhD students to recruit her patients. In particular, Chloe Farrell performed the epigenetic analyses on the present dataset, which have become a key component of my thesis work. Kelly Doolin also ran a wide range of biochemical procedures on our blood samples that will keep us investigating for years to come. My thanks also go to the other members of REDEEM for providing a lively working environment, which enriched me both professionally and personally: Chai Jairaj, Niamh O'Leary, Erik O'Hanlon, Clara Mai Fitzsimon, Amy Adair, Lucy Moran, and Darren Roddy.

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Lastly, I would like to mention the support I have received from family and friends throughout the duration of this PhD. Even across the distance that separated us, they have always encouraged me to pursue this goal to the best of my ability.

C

OWN PUBLICATIONS

During the three years of his PhD, the applicant contributed to the following works.

PUBLISHED ARTICLES

— **Tozzi L.**, Farrell C., Booij L., Doolin K., Nemoda Z., Szyf M., Pomares F.B., Chiarella J., O'Keane V., Frodl T. «Epigenetic Changes of FKBP5 as a Link Connecting Genetic and Environmental Risk Factors with Structural and Functional Brain Changes in Major Depression» In: *Neuropsychopharmachology*, 2017, doi: 10.1038/npp.2017.290

— McIntosh A., Gormley S., **Tozzi L.**, Frodl T., Harkin A. «Recent Advances in Translational Magnetic Resonance Imaging in Animal Models of Stress and Depression» In: *Frontiers in Cellular Neuroscience*, 2017, doi: 10.3389/fncel.2017.00150

— **Tozzi L.**, Doolin K., Farrel C., Joseph S., O'Keane V., Frodl T. «Functional Magnetic Resonance Imaging Correlates of Emotion Recognition and Voluntary Attentional Regulation in Depression: A Generalized Psycho-Physiological Interaction Study» In: *Journal of Affective Disorders*, 2017, doi: 10.1016/j.jad.2016.10.029

— Frodl T., Janowitz D., Schmaal L., **Tozzi L.**, Dobrowolny H. et al. «Childhood Adversity Impacts on Brain Subcortical Structures Relevant to Depression» In: *Journal of Psychiatric Research*, 2016, doi: 10.1016/j.jpsychires.2016.11.010

— **Tozzi L.**, Carballedo A., Lavelle G., Doolin k., Doyles M., Amico F., McCarthy H., Gormley J., Lord A., O'Keane V., Frodl T. «Longitudinal Functional Connectivity Changes Correlate with Mood Improvement after Regular Exercise in a Dose-Dependent Fashion» In: *The European Journal of Neuroscience*, 2016, doi: 10.1111/ejn.13222

— Wetterling F., McCarthy H., **Tozzi L.**, Skokauskas N., O'Doherty J.P., Mulligan A., Meaney J., Fagan, A., Gill M., Frodl T. «Impaired Reward Processing in the Human Prefrontal Cortex Distinguishes between Persistent and Remittent Attention Deficit Hyperactivity Disorder» In: *Human Brain Mapping*, 2016, doi: 10.1002/hbm.22944

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— **Tozzi L.**, Carballedo A., Wetterling F., McCarthy H., O'Keane V., Gill M., Morris D., Fahey C., Meaney J., Frodl T. «Single-Nucleotide Polymorphism of the FKBP5 Gene and Childhood Maltreatment as Predictors of Structural Changes in Brain Areas Involved in Emotional Processing in Depression» In: *Neuropsychopharmacology*, 2015, doi: 10.1038/npp.2015.170

POSTER PRESENTATIONS

— Lopez D., **Tozzi L.**, Joseph S., O'Keane V., Frodl T., Kerskens C. «Dynamic Magnetisation Transfer MRI in Major Depression Disorder: Delayed tissue response to cardiac pulsation in the basal ganglia» At: *International Society for Magnetic Resonance in Medicine meeting*, 2015, doi: 10.13140/RG.2.1.1978.0723

— **Tozzi L.**, Doolin K., Carballedo A., Lavelle G., Doyle M., McCarthy H., O'Keane V., Frodl T. «Improvement of well-being measures after regular physical exercise correlates with resting state connectivity in attentional and default mode networks» At: *European Neuropsychopharmacology meeting*, 2015, doi: 10.1016/S0924-977X(15)30380-1

— **Tozzi L.**, Carballedo A., Wetterling F., McCarthy H., Gill M., Morris D., O'Keane V., Fahey C., Meaney J., Frodl T. «Association between single nucleotide polymorphism of the FKBP5 gene and neural correlates of attentional bias towards emotional stimuli in depression» On: *Frontiers in Neuroscience*, 2014, doi: 10.3389/conf.fnins.2014.87.00014

STUDY INFORMATION, CONSENT AND SCALES

Contact Information

Name:_____ Date:_____

Address:_____

_____

Phone number:_____

Demographic Information

Date of Birth:_____/_____/_____ Age Today:_____

Gender: _____Male _____Female

Race/Ethnicity (check as many as apply):
_____Caucasian/White _____Asian/Pacific Islander _____Other (Please specify:
_____African/Black/Caribbean _____Hispanic/Latino _____)

Marital Status:
_____Single _____Married _____In partnership _____Divorced
_____Separated _____Widowed

Employment Status:
_____Employed Full Time _____Employed Part Time _____Student
_____On leave _____Unemployed

Highest Level of Education Achieved: _____

Health Information

Length of Current Depressive Episode: _____

Current Medications (List All) Date of commencement of antidepressant

_____

_____

_____

Height:_____ft_____in Weight:_____

Smoker: ___Yes ___No Alcohol: ___Yes ___No Other Drugs: ___Yes ___No
If Yes, units: _____ If Yes, specify: _____

For Recurrent Depression Study Only

Number of previous episodes: _____

Duration depression treated: _____

Duration depression not treated: _____

THE UNIVERSITY OF DUBLIN

TRINITY COLLEGE
SCHOOL OF MEDICINE
Tel.: 01-896-1000

European Commission

Title of research study:
Neuroimaging, stress hormone system and epigenetics
R'Birth: Return to Health: Human Imaging of Neuroplastic Changes in Depression
(EU International Research Funded)
International Project Leader: Professor Thomas Frodl, Trinity College Dublin & University of Regensburg, Germany,
local: Professor Veronica O'Keane, Trinity College Dublin

Health Research Board Funded (HRB) with regards to stress markers and association to imaging

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.
I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet
  Yes ☐ No ☐
- I have had the opportunity to ask questions and to discuss the study
  Yes ☐ No ☐
- I have received satisfactory answers to all my questions
  Yes ☐ No ☐
- I have received enough information about this study
  Yes ☐ No ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
  Yes ☐ No ☐
- I agree to take part in this study without prejudice to my legal or ethical rights
  Yes ☐ No ☐
- I filled out the MRI screening form
  Yes ☐ No ☐

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:
Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:
RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:
NAME OF SECOND WITNESS: SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's/Scientist's signature:
Date:
(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

THE UNIVERSITY OF DUBLIN

TRINITY COLLEGE
SCHOOL OF MEDICINE
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European Commission

INFORMATION SHEET

Title of the Project:

Neuroimaging, stress hormone system and epigenetics

R'Birth: Return to Health: Human Imaging of Neuroplastic Changes in Depression
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International Project Leader: Professor Thomas Frodl, Trinity College Dublin & University of Regensburg, Germany,
local: Professor Veronica O'Keane, Trinity College Dublin

Health Research Board Funded (HRB) with regards to stress markers and association to imaging

You are invited to take part in a research study. It is important for you to understand why this research is being carried out and which investigations it will involve, before you decide whether you would like to take part. This Information Sheet has been written for you and it is essential that you read through it carefully and discuss with your doctor, one of the researchers or anybody you wish. Please ask whatever you want to ask. Further information about the study can be provided. Take time to decide whether or not you wish to take part.

PURPOSE OF THE STUDY:

You are invited to participate in a research study. You were selected as a possible participant in this study either because you are having depression or as a control participant.

The aim of the study is to identify diagnostic markers for the disease and for the risk to develop major depression using neuroimaging (magnetic resonance imaging (MRI), genetics, epigenetics and stress hormone markers. To do this we are asking you to take part in an MRI investigation, in a clinical interview on the history and acute symptomatology of your disease (for patients) and to give blood and saliva samples.

We hope to identify, structural and functional changes in the brain of patients with clinical depression, how these are related to the risk to develop the disease and how stress and genetic risk interplay to result in these changes. We will also ask you for a blood sample to examine genetic and stress factors that might be involved.

The blood and saliva samples, and brain scans that we obtain from you will be used for this study and closely related studies seeking to find the changes that major depression produces.

You will be required to visit once or twice to the Institute of Neuroscience at Trinity College to have an MRI, clinical testings and blood samples taken. Professor Veronica O'Keane's team will follow you up in the Mary Mercier Clinic, or Sheaf House or any other agreed location.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have either major depression or are a healthy person.

DO I HAVE TO TAKE PART?

It is your decision whether you take part or not. If you decide to get involved with the study, this Information Sheet will be handed out and will be explained to you. You will be asked to sign the Consent Form. You may withdraw from the study at any time you wish and without giving a reason. This will not affect the care you receive from your doctor or any other person with whom you are involved.

WHAT WILL HAPPEN IF I AGREE TO TAKE PART IN THIS STUDY?

If you decide to participate, we will ask you to go to Trinity college and interviews and questionnaires to assess your current symptoms will be completed. This will take about 60 minutes. During this appointment a doctor or nurse will take the blood samples.

Moreover, a magnetic resonance imaging (MRI), including a so called functional magnetic resonance imaging (fMRI), diffusion tensor imaging and MRI spectroscopy scan, will be done at the Institute of Neuroscience located at Lloyd Building in Trinity College Dublin. The MRI machine uses a magnetic field to take pictures of the brain. Before you enter the room where the machine is located, you will have to remove all the metallic things you may be wearing such as bracelets, earrings, watch, or keys. You will be asked to lie on a long narrow couch for about 60 minutes while the MRI machine gathers information. The couch is within a wider tube, so that you may feel a bit confined. If you feel claustrophobic while lying on the couch, you can stop the scan at any time. Each scan may take between 5 and 15 minutes and during this time you will hear tapping noises. As the noise can sometimes be loud, we will give you earplugs so that the noise is reduced. While lying on the couch, we will place pads around your head so that it remains still. The padding is to help you keep your head still. You will be able to speak and move your head if it becomes uncomfortable.

While you are lying on the couch, you will be able to speak with the operator of the scanner at any time. In addition, you will have a button in your hand that you can use to stop the measurement at any time.

You will be asked to look at pictures on a screen while lying on the couch. While viewing these pictures you have to provide answers by pressing a button in your hand. What you need to do will be explained to you before you go to the scanner and you will have the opportunity to see a short example of the test.

There are no drugs involved in the study.

The blood samples you give will be examined by our staff at our genetic research laboratory in St. James's Hospital, Trinity Health Centre and in the Trinity College Institute of Neuroscience Dublin and by our collaboration partners of McGill University Montreal as well as BGI Europe. The staff at the MRI centre of St. James Hospital and the staff of our research group will know the identity of your blood sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Veronica O'Keane and Professor Thomas Frodl, Trinity College Dublin. The blood will be analysed for genetic as well as epigenetic (effects of environment on the gene) individual information. At a later stage these results may form part of a collaborative study with researchers in Ireland and abroad.

WHAT WILL BE THE POSSIBLE BENEFITS OF TAKING PART?

This study will be of no direct benefit to you, but will be used to help identify biological parameters that would diagnose the presence and the risk of major depression. It is expected that important diagnostic and treatment changes will emerge in the future, as a result of these discoveries. No individual genetic or non-genetic (protein expression) result will be available from the study, to you or to anyone else, and this study does not involve screening for genetic diseases.
If you wish, we will keep you informed of the progress of the study in general.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

The risk for the blood sample is a standard clinical procedure and very safe. There may be minor pain with the procedure but it will be localized and of short duration. Occasionally there is an infection, and if so, it will be treated.

This MRI machine uses a strong magnet to make images of the brain. You will be asked to lie on a long narrow couch for about 60 minutes while the machine gathers data. During this time you will be exposed to a magnetic field which you will not feel. You will, however, hear repetitive tapping noises that arise from the scanner around your body. We will provide earplugs and headphones that you will be required to wear so that it is not too loud. The space within the large magnet in which you lie is somewhat narrow, although we have taken many steps to relieve the "claustrophobic" feeling.

There are no known significant risks with this procedure since the main magnetic field at the strengths used are felt to be without harm. There are conservative guidelines for radiofrequency magnetic fields and main magnetic field exposure and our examinations fall within those guidelines. We feel these are safe levels and less hazardous than a comparable x-ray computed tomography examination.

MRI can be also obtained in pregnant women and for foetal diagnosis, however, this will be avoided in the present study.

People who cannot be scanned using MRI include persons who have a cardiac pacemaker or a certain type of metallic clip in their body (i.e., an aneurysm clip in the brain); persons who have worked with metal or had a piece of metal removed from the eye(s); or persons who have shrapnel, bullets, or buckshot in their body.

There is a risk of heating from the imaging coils, and/or the cables from monitoring devices that record physiologic processes such as heart beats per minute. Please report any heating sensation immediately. You may have the scan stopped at any time if this occurs.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and shouldn't be painful. However, you may have the scan stopped at any time if this occurs.

Dizziness and nausea may occur if the head is moved rapidly while you are lying on the couch.

Please take note that some subjects have experienced claustrophobia; you may discontinue the scan at anytime.

You will be told if any new information is learned which may affect your condition or influence your willingness to continue participation in this study.

While participating in this study, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, effects of research drugs, or similar hazards. The alternative to participation is not to participate.

WILL MY TAKING PART BE CONFIDENTIAL?

Yes.

All information, which is collected about you, during the course of the research, will be kept strictly confidential. Your name will not be attached to any information about you that leaves the hospital.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be published in scientific journals and presented at conferences, again without any breach of confidentiality.

LEGAL ISSUES:

The doctors involved in this study are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

THE UNIVERSITY OF DUBLIN

TRINITY COLLEGE
SCHOOL OF MEDICINE
Tel.: 01-896-1000

European Commission

PERMISSION:
This study has been approved by the St. James's and AMNCH Committee

FURTHER INFORMATION:
If you would like to obtain further information about the nature of the study you can do so by contacting:

Prof. Veronica O'Keane
Department of Psychiatry
Tallaght Psychiatry Services
Sheaf House
Belgard Square Nord
Tallaght
Dublin 24
Ireland
Tel: 01 463 5200

Professor Thomas Frodl
Department of Psychiatry
Centre for General Psychiatry II, University of Regensburg
Clinical Director
Universitaetstr. 84
93051 Regensburg
Germany,
Tel.: 0049-941-9412017

Thank you for your help with this project.

MAGNETIC RESONANCE IMAGING

TRINITY COLLEGE
Institute of Neuroscience
TCIN *from molecules to mind*

Name: _____

Phone- _____

Sex: Male [ ] Female [ ]

Date of Birth: _____

Weight: _____kg

Please provide us with the details of another person (e.g., next-of-kin) should we need to contact you in the future.

Name of contact person: _____

Phone: _____

Study: New approaches to functional Magnetic Resonance Imaging in the human brain.

Time in: ____:____ Time Out: ____:____

Investigator: _____

Information:

The MRI scan being done is designed to answer research questions, not examine your brain medically. This MRI scan is not a substitute for one a doctor would order. It may not show problems that would be picked up by a medical MRI scan.

There are some items that may interfere with the Magnetic Resonance Imaging and some that may be potentially hazardous. To help us to determine your suitability for an MRI scan and to ensure your safety, please complete the following checklist carefully. Not all people can have an MRI scan because the strong magnetic field may be hazardous to them.

- **People with**
- **permanent pacemakers**
- **prosthetic heart valves**
- **implanted cardiac defibrillators**
- **certain types of vascular clips**

Cannot have an MRI scan

Instructions for Patient/Volunteers

1. You are urged to use the earplugs or headphones we supply during your MRI examination since some patients may find the noise levels unacceptable, and the noise levels may affect your hearing.
2. Remove all jewelry (eg, necklaces, pins, rings).
3. Remove all hairpins, bobby pins, barrettes, clips, etc.
4. Remove all dentures, false teeth, and partial dental plates.
5. Remove hearing aides.
6. Remove eyeglasses.
7. Remove your watch, pager, cell phone, credit cards, bankcards, and all other cards with a magnetic strip.
8. Remove body piercing objects.
9. Use gown, if provided, or remove all clothing with metal fasteners, zippers, etc.

CHECK LIST FOR 3T MAGNETIC RESONANCE IMAGING

Do you have any of the following:

Cardiac Pacemaker: Yes No
Have you ever had any surgical procedures? Yes No

If yes, what type and where

.....

.....

The following items may be harmful to you during your MR scan or may interfere with the MR examination. You must provide a "yes" or "no" for every item. Please indicate if you have or have had any of the following:

Yes	No	
____	____	Any type of electronic, mechanical, or magnetic implant Type:
____	____	Cardiac pacemaker
____	____	Aneurysm clip
____	____	Implanted cardiac defibrillator
____	____	Neurostimulator
____	____	Biostimulator Type:
____	____	Any type of internal electrodes or wires
____	____	Cochlear implant
____	____	Hearing aid
____	____	Implanted drug pump (eg, insulin, Baclofen, chemotherapy, pain medicine)
____	____	Halo vest
____	____	Spinal fixation device
____	____	Spinal fusion procedure
____	____	Any type of coil, filter, or stent Type:
____	____	Any type of metal object (eg, shrapnel, bullet, BB)
____	____	Artificial heart valve
____	____	Any type of ear implant
____	____	Penile implant
____	____	Artificial eye
____	____	Eyelid spring
____	____	Any type of implant held in place by a magnet Type:
____	____	Any type of surgical clip or staple
____	____	Any IV access port (eg, Broviac, Port-a-Cath, Hickman, Picc line)
____	____	Medication patch (eg, nitroglycerine, nicotine)
____	____	Shunt
____	____	Artificial limb or joint What and where:
____	____	Tissue expander (eg, breast)
____	____	Removable dentures, false teeth, or partial plate
____	____	Diaphragm, IUD, Pessary Type:
____	____	Surgical mesh Location:
____	____	Body piercing Location:
____	____	Wig, hair implants
____	____	Tattoos or tattooed eyeliner
____	____	Claustrophobia

Native Language: _____

For female participants it is also important that you tell us if there is any possibility that you are pregnant. To date there are no known risks of MRI during pregnancy, however as a precautionary safety measure pregnant individuals will not be included in the study. To participate in the current study women of child-bearing potential must be using one of the following acceptable methods of birth-control:

a. oral or transdermal contraceptives
b. barrier (diaphragm or condom) with spermicide
c. intrauterine progesterone contraceptive system
d. levonorgestrel implant
e. medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual activity

Do you meet these requirements?

Yes No

____ ____

I have read and understood this form, and consent to my study being used for research. I have had a chance to ask any questions.

Signed (Volunteer): _____

Witnessed (Researcher/MR staff): _____

Date: _____

TRINITY COLLEGE
Institute of Neuroscience
TCIN *from molecules to mind*

GENERAL MRI DATA CONSENT FORM

Trinity College Institute of Neuroscience, (TCIN) is performing research, utilising an MRI scanner at Trinity College, Dublin 2. These research scans, although not full clinical scans, will be read by a radiologist.
In the unlikely event of an irregularity being found, the radiologist, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght] will inform the participants GP, that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.
To enable us to perform the research scans the participant agrees to give consent/ permission for:

(i) TCIN to conduct the MRI scan and store MRI scan data of participant;
(ii) TCIN or Principal Investigator, (PI) to contact participants GP;
(iii) TCIN radiographer to send MRI scan data to radiologist acting for TCIN;
(iv) Radiologist to store data in a hospital system with same care as other patient data ensuring participants confidentiality;
(v) Radiologist/ Clinician (acting for TCIN) to contact participants GP;
(vi) TCIN to store data on the study for a period of at least 5 years or as specified in the specific consent form.

A dated standard letter signed by the appropriate Principal Investigator will be sent to all participants GP's, it is the responsibility of the Principal Investigator to ensure that this is sent at least two days before scanning to allow for postal delays. The principal investigator is responsible for their project at all times.

The TCIN designated radiologist will be sent data in a form that allows identification so that if a response is required he can act quickly. This will be stored in the hospital system with the same rigour and attention to confidentiality as all other medical data, as per the rules of that institution. The raw scan data will be stored at TCIN in anonymous form for research purposes as agreed on the consent form of the specific research project.

I agree to the above points and understand that my data will be treated carefully at TCIN and in the hospital system.

Participant Name and Address_____

_____

_____

Signed by Participant:_____

Participants GP Name and Address

_____

_____

Date:_____

Below (i) is the standard letter to be sent to all participants GP's:

(i) Standard letter to GP from Trinity College Institute of Neuroscience.

Participant '_____' is taking part in a research study, utilising an MRI scanner at Trinity College Institute of Neuroscience, TCD Dublin 2. These research scans, although not full clinical scans, will be read by a clinician.

In the event of an irregularity being found, the clinician, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital] will inform you as the participants GP that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

The GP should then contact the participant to advise them that a proper clinical scan, at a hospital, is recommended to check the irregularity.

In the unlikely event that you need to contact us, the following telephone number can be used. (01-8962925).

This letter was posted to the participants GP on___/___/_____(Day/Month/Year). Copy of this to be given to TCIN radiographer before scanning takes place.

*Signature of PI.*_____

NAME: _____ DATE: _____

A. MAJOR DEPRESSIVE EPISODE

(→ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS **A1** OR **A2** CODED **YES**?	→NO	YES

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE YES.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS **(A1-A3)** CODED **YES**?

NO	YES *
MAJOR DEPRESSIVE EPISODE, CURRENT	

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

A4 a During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? →NO YES

b In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?

NO	YES
MAJOR DEPRESSIVE EPISODE, RECURRENT	

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(→ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:

A5 a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
	IS EITHER **A5a** OR **A5b** CODED **YES**?	→NO	YES

A6	**Over the past two week period, when you felt depressed and uninterested:**		
a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
b	Did you feel regularly worse in the morning, almost every day?	NO	YES
c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED YES?

NO	YES
	Major Depressive Episode **with** ***Melancholic Features Current***

B. DYSTHYMIA

(→ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	→NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	→YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	→NO	YES

B4 Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?

NO	YES
	DYSTHYMIA **CURRENT**

C. SUICIDALITY

In the past month did you:

				Points
C1	Suffer any accident? IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:	NO	YES	0
C1a	Plan or intend to hurt yourself in that accident either passively or actively? IF NO TO C1a, SKIP TO C2: IF YES, ASK C1b,:	NO	YES	0
C1b	Did you intend to die as a result of this accident?	NO	YES	0
C2	Think that you would be better off dead or wish you were dead?	NO	YES	1
C3	Want to harm yourself or to hurt or to injure yourself?	NO	YES	2
C4	Think about suicide?	NO	YES	6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency	Intensity
Occasionally	Mild
Often	Moderate
Very often	Severe

→ Can you control these impulses and state that you will not act on them while in this program? Only score 8 points if response is NO. NO YES 8

C5	Have a suicide plan?	NO	YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
C7	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
C8	Attempt suicide? Hoped to be rescued / survive Expected / intended to die	NO	YES	10

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT C1) CODED YES?

NO **YES**

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

SUICIDE RISK CURRENT

1-8 points Low
9-16 points Moderate
≥ 17 points High

Hamilton Depression Rating Scale (HAM-D)

Name: _____ Date of Assessment: _____

Age: _____ Gender: _____Male _____Female

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

☐ 1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0=Absent
1=Sadness, etc.
2=Occasional weeping
3=Frequent weeping
4=Extreme symptoms

☐ 2. FEELINGS OF GUILT
0=Absent
1=Self-reproach, feels he/she has let people down
2=Ideas of guilt
3=Present illness is a punishment; delusions of guilt
4=Hallucinations of guilt

☐ 3. SUICIDE
0=Absent
1=Feels life is not worth living
2=Wishes they were dead or any thoughts of possible death to self
3=Suicidal ideas or gestures
4=Attempts at suicide

☐ 4. INSOMNIA – Initial
(Difficulty falling asleep)
0=Absent
1=Occasional
2=Frequent

☐ 5. INSOMNIA – Middle
(Complains of being restless and disturbed during the night. Waking during the night.)
0=Absent
1=Occasional
2=Frequent

☐ 6. INSOMNIA – Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0=Absent
1=Occasional
2=Frequent

☐ 7. WORK AND INTERESTS
0=No difficulty
1=Feelings of incapacity, listlessness, indecision and vacillation
2=Loss of interest in hobbies, decreased social activities
3=Productivity decreased
4=Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score)

☐ 8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor)
0=Absent
1=Occasional
2=Frequent

9. AGITATION
(Restlessness associated with anxiety.)
☐ 0=Absent
1=Occasional
2=Frequent

10. ANXIETY – PSYCHIC
☐ 0=No difficulty
1=Tension and irritability
2=Worrying about minor matters
3=Apprehensive attitude
4=Fears

☐ 11. ANXIETY – SOMATIC
(Indigestion, cramps, palpitations, headaches, hyperventilation, sweating, tremor)
0=Absent
1=Mild
2=Moderate
3=Severe
4=Incapacitating

☐ 12. SOMATIC SYMPTOMS – GASTROINTESTINAL
0=Absent
1=Loss of appetite but eating without encouragement from others
2=Difficulty eating without urging from others, marked reduction of food intake

☐ 13. SOMATIC SYMPTOMS – GENERAL
0=Absent
1=Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2=Any clear-cut symptom rates 2

☐ 14. GENITAL SYMPTOMS (Loss of libido, impaired sexual performance, menstrual disturbances)
0=Absent
1=Mild
2=Severe

☐ 15. HYPOCHONDRIASIS
0=Not present
1=Self-absorption
2=Preoccupation with health
3=Querulous attitude
4=Hypochondriacal delusion

☐ 16. WEIGHT LOSS
0=No weight loss
1=Slight
2=Obvious

☐ 17. INSIGHT
(Insight must be interpreted in terms of patient's understanding and background.)
0=No loss
1=Partial or doubtful loss
2=Loss of insight

TOTAL ITEMS 1 TO 17: _____
0 – 7 = Normal
8 – 13 = Mild Depression
14 – 18 = Moderate Depression
19 – 22 = Severe Depression
≥ 23 = Very Severe Depression

☐ 18. DIURNAL VARIATION
(Symptoms worse in the morning or evening. Note which it is.)
0=No Variation
1=Mild variation; AM ( ) PM ( )
2=Severe variation; AM ( ) PM ( )

☐ 19. DEPERSONALIZATION AND DEREALIZATION
(Feelings of unreality, nihilistic ideas)
0=Absent
1=Mild
2=Moderate
3=Severe
4=Incapacitating

☐ 20. PARANOID SYMPTOMS
(Not with a depressive quality)
0=None
1=Suspicious
2=Ideas of reference
3=Delusions of reference and persecution
4=Hallucinations, persecutory

☐ 21. OBSESSIONAL SYMPTOMS
(Obsessive thoughts and compulsions against which the patient struggles)
0=Absent
1=Mild
2=Severe

ATYPICAL FEATURES:

Check if any of the following are true:

☐ A. Mood Reactivity (mood brightens in response to actual or potential positive events)

☐ B. At least two of the following:
Significant weight gain or increase of appetite
Hypersomnia (Sleeping too much)
Leaden paralysis (Heavy feeling of arms and legs)
Longstanding pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment.

If both A and B are true, depression is atypical.

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood [0] [1] [2] [3] [4]

Worries, anticipation of the worst, fearful anticipation, irritability.

2 Tension [0] [1] [2] [3] [4]

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 Fears [0] [1] [2] [3] [4]

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 Insomnia [0] [1] [2] [3] [4]

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 Intellectual [0] [1] [2] [3] [4]

Difficulty in concentration, poor memory.

6 Depressed mood [0] [1] [2] [3] [4]

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 Somatic (muscular) [0] [1] [2] [3] [4]

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 Somatic (sensory) [0] [1] [2] [3] [4]

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 Cardiovascular symptoms [0] [1] [2] [3] [4]

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 Respiratory symptoms [0] [1] [2] [3] [4]

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 Gastrointestinal symptoms [0] [1] [2] [3] [4]

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 Genitourinary symptoms [0] [1] [2] [3] [4]

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13 Autonomic symptoms [0] [1] [2] [3] [4]

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 Behavior at interview [0] [1] [2] [3] [4]

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the past **two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

Subtotal Page 1
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11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Subtotal Page 2

Subtotal Page 1

Total Score

Name: _____
Age: _____ Gender: _____Male _____Female
Date: _____

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you...	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason:				
6. During the past month, how often have you taken medicine (prescribed or "over the counter" to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Scoring the Pittsburgh Sleep Quality Index

Component 1 #9 Score _____

Component 2 #2 Score (≤15min=0; 16-30min=1; 31-60min=2; >60min=3) + #5a Score
(if sum is equal to 0=0; 1-2=1; 3-4=2; 5-6=3) _____

Component 3 #4 Score (≥7=0; 6-7=1; 5-6=2; <5=3) _____

Component 4 (total # of hours asleep)/(total # of hours in bed) x 100
>85%=0; 75%-84%=1; 65%-74%=2; <65%=3 _____

Component 5 Sum of scores #5b to #5j (0=0; 1-9=1; 10-18=2, 19-27=3) _____

Component 6 #6 Score _____

Component 7 #7 Score + #8 Score (0=0; 1-2=1; 3-4=2; 5-6=3)

Add the seven component scores together for **the Global PSQI Score** _____

CTQ

Name: _____

Age: _____

Gender: _____Male _____Female

When I was growing up...	Never True	Rarely True	Some-times True	Often True	Very Often True
1. I didn't have enough to eat.					
2. I knew that there was someone to take care of me and protect me					
3. People in my family called me things like "stupid," "lazy," or "ugly."					
4. My parents were too drunk or high to take care of the family.					
5. There was someone in my family who helped me feel that I was important or special.					
6. I had to wear dirty clothes.					
7. I felt loved.					
8. I thought that my parents wished I had never been born.					
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.					
10. There was nothing I wanted to change about my family.					
11. People in my family hit me so hard that it left me with bruises or marks.					
12. I was punished with a belt, a board, a cord, or some other hard object.					
13. People in my family looked out for each other.					
14. People in my family said hurtful or insulting things to me.					
15. I believe that I was physically abused.					
16. I had the perfect childhood.					
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.					
18. I felt that someone in my family hated me.					
19. People in my family felt close to each other.					
20. Someone tried to touch me in a sexual way, or tried to make me touch them.					
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
22. I had the best family in the world.					
23. Someone tried to make me do sexual things or watch sexual things.					
24. Someone molested me.					
25. I believe that I was emotionally abused.					
26. There was someone to take me to the doctor if I needed it.					
27. I believe that I was sexually abused.					
28. My family was a source of strength and support.					

CAMI SEQUENCES DETAILS

CAMI T1 sequence details

```
SmartSelect =                   "yes";
Coil 1  (exclude) =             "None";
Uniformity =                    "CLEAR";
FOV          FH (mm) =          256;
             AP (mm) =          256;
             RL (mm) =          160;
Voxel size   FH (mm) =          1;
             AP (mm) =          1;
             RL (mm) =          1;
Recon voxel size (mm) =         1;
Fold-over suppression =         "no";
Slice oversampling =            "default";
Reconstruction matrix =         256;
SENSE =                         "yes";
    P reduction (AP) =          1;
    S reduction (RL) =          1.5;
k-t BLAST =                     "no";
Overcontiguous slices =         "no";
Stacks =                        1;
    slices =                    160;
    slice orientation =         "sagittal";
    fold-over direction =       "AP";
    fat shift direction =       "F";
Stack Offc. AP (P=+mm) =        -15.0076456;
            RL (L=+mm) =        -1.71528864;
            FH (H=+mm) =        -20.5721664;
      Ang.  AP (deg) =          -1.57631814;
            RL (deg) =          0.163514286;
            FH (deg) =          -1.75226152;
      Free rotatable =          "no";
Multi-chunk =                   "no";
Large table movement =          "no";
PlanAlign =                     "no";
REST slabs =                    0;
Interactive positioning =       "no";
Patient position =              "head first";
        orientation =           "supine";
Scan type =                     "Imaging";
Scan mode =                     "3D";
    technique =                 "FFE";
Contrast enhancement =          "T1";
Acquisition mode =              "cartesian";
Fast Imaging mode =             "TFE";
    shot mode =                 "multishot";
TFE factor =                    240;
    startup echoes =            "default";
    shot interval =             "user defined";
        (ms) =                  3000;
    profile order =             "linear";
    turbo direction =           "Y";
Echoes =                        1;
    partial echo =              "no";
    shifted echo =              "no";
TE =                            "user defined";
    (ms) =                      3.9000001;
Flip angle (deg) =              8;
TR =                            "user defined";
    (ms) =                      8.5;
Halfscan =                      "no";
Water-fat shift =               "maximum";
Shim =                          "auto";
mDIXON =                        "no";
Fat suppression =               "no";
Water suppression =             "no";
TFE prepulse =                  "invert";
    slice selection =           "no";
    delay =                     "shortest";
    PSIR =                      "no";
MTC =                           "no";
```

```
T2prep =                          "no";
Diffusion mode =                  "no";
Multi-transmit =                  "no";
SAR mode =                        "high";
B1 mode =                         "default";
PNS mode =                        "low";
Gradient mode =                   "default";
SofTone mode =                    "no";
Cardiac synchronization =         "no";
Respiratory compensation =        "no";
Navigator respiratory comp =      "no";
Flow compensation =               "no";
fMRI echo stabilisation =         "no";
NSA =                             1;
Angio / Contrast enh. =           "no";
Quantitative flow =               "no";
CENTRA =                          "no";
Manual start =                    "no";
Dynamic study =                   "no";
Arterial Spin labeling =          "no";
Preparation phases =              "auto";
Interactive F0 =                  "no";
B0 field map =                    "no";
MIP/MPR =                         "no";
SWIp =                            "no";
Images =                          "M", (3) "no";
Autoview image =                  "M";
Calculated images =               (4) "no";
Reference tissue =                "Grey matter";
Recon compression =               "No";
Preset window contrast =          "soft";
Reconstruction mode =             "real time";
Save raw data =                   "no";
Hardcopy protocol =               "no";
Image filter =                    "system default";
Geometry correction =             "default";
Elliptical k-space shutter =      "default";
IF_info_seperator =               1634755923;
Total scan duration =             "07:32.1";
Rel. SNR =                        1;
Act. TR/TE (ms) =                 "8.5 / 3.9";
ACQ matrix M x P =                "256 x 240";
ACQ voxel MPS (mm) =              "1.00 / 1.07 / 1.00";
REC voxel MPS (mm) =              "1.00 / 1.00 / 1.00";
Scan percentage (%) =             93.75;
TFE shots =                       150;
TFE dur. shot / acq (ms) =        "2089.6 / 2040.5";
Min. TI delay =                   1060.17468;
Act. WFS (pix) / BW (Hz) =        "2.420 / 179.4";
Min. WFS (pix) / Max. BW (Hz) =   "0.559 / 776.8";
Min. TR/TE (ms) =                 "8.5 / 3.7";
SAR / head =                      "<  7 %";
Whole body / level =              "0.0 W/kg / normal";
SED =                             "  0.0 kJ/kg";
B1+rms =                          "0.62 uT";
Max B1+rms =                      "0.62 uT";
PNS / level =                     "55 % / normal";
dB/dt =                           "59.4 T/s";
Sound Pressure Level (dB) =       9.72935867;
```

CAMI fMRI sequence details

```
SmartSelect =                   "yes";
Coil 1  (exclude) =             "None";
Uniformity =                    "CLEAR";
FOV          RL (mm) =          230;
             AP (mm) =          230;
             FH (mm) =          110.400002;
Voxel size   RL (mm) =          3;
             AP (mm) =          3;
Slice thickness (mm) =          4.80000019;
Recon voxel size (mm) =         2.875;
Fold-over suppression =         "no";
Reconstruction matrix =         80;
SENSE =                         "yes";
    P reduction (AP) =          1.79999995;
k-t BLAST =                     "no";
Stacks =                        1;
    type =                      "parallel";
    slices =                    23;
    slice gap =                 "user defined";
          gap (mm) =            0;
    slice orientation =         "transverse";
    fold-over direction =       "AP";
    fat shift direction =       "P";
Stack Offc. AP (P=+mm) =        4.83997059;
            RL (L=+mm) =        -1.71528864;
            FH (H=+mm) =        -6.42739153;
      Ang.  AP (deg) =          -1.57631814;
            RL (deg) =          -15.0199013;
            FH (deg) =          -1.75226152;
      Free rotatable =          "no";
Minimum number of packages =    1;
Slice scan order =              "ascend";
Large table movement =          "no";
PlanAlign =                     "no";
REST slabs =                    0;
Shim  Size  AP (mm) =           166.92659;
            RL (mm) =           123.51709;
            FH (mm) =           130.400009;
      Offc. AP (P=+mm) =        0.588481724;
            RL (L=+mm) =        -0.787108362;
            FH (H=+mm) =        -5.26017952;
      Ang.  AP (deg) =          -1.57631814;
            RL (deg) =          -15.0199013;
            FH (deg) =          -1.75226152;
Interactive positioning =       "no";
Patient position =              "head first";
        orientation =           "supine";
Scan type =                     "Imaging";
Scan mode =                     "MS";
    technique =                 "SE";
Modified SE =                   "no";
Acquisition mode =              "cartesian";
Fast Imaging mode =             "EPI";
    shot mode =                 "single-shot";
Echoes =                        1;
    partial echo =              "no";
TE =                            "user defined";
    (ms) =                      35;
Flip angle (deg) =              90;
TR =                            "user defined";
    (ms) =                      2000;
Halfscan =                      "no";
Water-fat shift =               "minimum";
Shim =                          "PB-volume";
ShimAlign =                     "yes";
mDIXON =                        "no";
Fat suppression =               "SPIR";
   strength =                   "strong";
   frequency offset =           "user defined";
```

```
       offset (Hz) =            250;
Water suppression =             "no";
BB pulse =                      "no";
MTC =                           "no";
Diffusion mode =                "no";
Multi-transmit =                "no";
SAR mode =                      "high";
B1 mode =                       "default";
PNS mode =                      "high";
Gradient mode =                 "maximum";
SofTone mode =                  "no";
Cardiac synchronization =       "no";
Respiratory compensation =      "no";
Navigator respiratory comp =    "no";
Flow compensation =             "no";
Temporal slice spacing =        "minimal";
NSA =                           1;
Manual start =                  "yes";
Dynamic study =                 "individual";
    dyn scans =                 550;
    dyn scan times =            "shortest";
    fov time mode =             "default";
    dummy scans =               2;
    immediate subtraction =     "no";
    fast next scan =            "no";
    synch. ext. device =        "yes";
        start at dyn. =         1;
        interval (dyn) =        1;
    dyn stabilization =         "regular";
    prospect. motion corr. =    "no";
Keyhole =                       "no";
Arterial Spin labeling =        "no";
Preparation phases =            "full";
Interactive F0 =                "no";
B0 field map =                  "no";
MIP/MPR =                       "no";
Images =                        "M", (3) "no";
Autoview image =                "M";
Calculated images =             (4) "no";
Reference tissue =              "Grey matter";
Recon compression =             "No";
Preset window contrast =        "soft";
Reconstruction mode =           "real time";
    reuse memory =              "no";
Save raw data =                 "no";
Hardcopy protocol =             "no";
Image filter =                  "system default";
Geometry correction =           "default";
IF_info_seperator =             1634755923;
Total scan duration =           "18:34.6";
Rel. SNR =                      1;
Act. TR (ms) =                  "2000";
Act. TE (ms) =                  "35";
Dyn. scan time =                "00:02.0";
ACQ matrix M x P =              "76 x 76";
ACQ voxel MPS (mm) =            "3.03 / 3.03 / 4.80";
REC voxel MPS (mm) =            "2.88 / 2.88 / 4.80";
Scan percentage (%) =           100;
Packages =                      1;
Min. slice gap (mm) =           -0;
EPI factor =                    43;
WFS (pix) / BW (Hz) =           "8.058 / 53.9";
BW in EPI freq. dir. (Hz) =     "3646.3";
Min. TR (ms) =                  "1347";
SPIR offset act./default (Hz) = "250 [220]";
SAR / head =                    "<  44 %";
Whole body / level =            "< 0.1 W/kg / normal";
SED =                           "< 0.1 kJ/kg";
B1+rms =                        "1.55 uT";
Max B1+rms =                    "1.55 uT";
PNS / level =                   "100 % / 1st level";
dB/dt =                         "107.5 T/s";
```

```
Sound Pressure Level (dB) =     28.1904297;
```

CAMI diffusion sequence details

```
SmartSelect =                   "yes";
Coil 1  (exclude) =             "None";
Uniformity =                    "CLEAR";
FOV          RL (mm) =          200;
             AP (mm) =          259.259247;
             FH (mm) =          125.999992;
Voxel size   RL (mm) =          1.875;
             AP (mm) =          1.88;
Slice thickness (mm) =          2.0999999;
Recon voxel size (mm) =         1.80041146;
Fold-over suppression =         "no";
Reconstruction matrix =         144;
SENSE =                         "yes";
    P reduction (AP) =          2.5;
k-t BLAST =                     "no";
Stacks =                        1;
    type =                      "parallel";
    slices =                    60;
    slice gap =                 "user defined";
          gap (mm) =            0;
    slice orientation =         "transverse";
    fold-over direction =       "AP";
    fat shift direction =       "P";
Stack Offc. AP (P=+mm) =        4.83997059;
            RL (L=+mm) =        -1.71528864;
            FH (H=+mm) =        -6.42739153;
      Ang.  AP (deg) =          -1.57631814;
            RL (deg) =          -15.0199013;
            FH (deg) =          -1.75226152;
      Free rotatable =          "no";
Minimum number of packages =    1;
Slice scan order =              "default";
Large table movement =          "no";
PlanAlign =                     "no";
REST slabs =                    0;
Shim  Size  AP (mm) =           166.92659;
            RL (mm) =           123.51709;
            FH (mm) =           146;
      Offc. AP (P=+mm) =        0.588481724;
            RL (L=+mm) =        -0.787108362;
            FH (H=+mm) =        -5.26017952;
      Ang.  AP (deg) =          -1.57631814;
            RL (deg) =          -15.0199013;
            FH (deg) =          -1.75226152;
Interactive positioning =       "no";
Patient position =              "head first";
        orientation =           "supine";
Scan type =                     "Imaging";
Scan mode =                     "MS";
    technique =                 "SE";
Modified SE =                   "no";
Acquisition mode =              "cartesian";
Fast Imaging mode =             "EPI";
    shot mode =                 "single-shot";
Echoes =                        1;
    partial echo =              "no";
TE =                            "user defined";
    (ms) =                      59;
Flip angle (deg) =              90;
TR =                            "shortest";
Halfscan =                      "yes";
    factor =                    0.680851042;
Water-fat shift =               "minimum";
Shim =                          "PB-volume";
ShimAlign =                     "yes";
mDIXON =                        "no";
Fat suppression =               "SPIR";
   strength =                   "strong";
   frequency offset =           "user defined";
```

```
       offset (Hz) =            250;
Grad Rev Fat suppression =      "no";
Water suppression =             "no";
BB pulse =                      "no";
MTC =                           "no";
Diffusion mode =                "DTI";
    gradient duration =         "minimum";
    gradient overplus =         "no";
    directional resolution =    "from file";
    average high b =            "no";
Multi-transmit =                "no";
SAR mode =                      "high";
B1 mode =                       "default";
PNS mode =                      "moderate";
Gradient mode =                 "enhanced";
SofTone mode =                  "no";
Cardiac synchronization =       "no";
Respiratory compensation =      "no";
Navigator respiratory comp =    "no";
Flow compensation =             "no";
Temporal slice spacing =        "equidistant";
NSA =                           1;
Manual start =                  "yes";
Dynamic study =                 "no";
    dyn stabilization =         "regular";
Arterial Spin labeling =        "no";
Preparation phases =            "full";
Interactive F0 =                "no";
B0 field map =                  "no";
MIP/MPR =                       "no";
Images =                        "M", (3) "no";
Autoview image =                "M";
Calculated images =             (4) "no";
Reference tissue =              "Grey matter";
Recon compression =             "No";
Preset window contrast =        "soft";
Reconstruction mode =           "immediate";
Save raw data =                 "no";
Hardcopy protocol =             "no";
Image filter =                  "system default";
Geometry correction =           "default";
IF_info_seperator =             0;
```

TCIN T1 sequence details

```
SmartSelect =                   "yes";
Coil 1  (exclude) =             "None";
Uniformity =                    "CLEAR";
FOV          AP (mm) =          230;
             RL (mm) =          230;
             FH (mm) =          162;
Voxel size   AP (mm) =          0.8984375;
             RL (mm) =          0.8984375;
             FH (mm) =          0.899999976;
Recon voxel size (mm) =         0.8984375;
Fold-over suppression =         "no";
Slice oversampling =            "default";
Reconstruction matrix =         256;
SENSE =                         "yes";
    P reduction (RL) =          2.29999995;
    S reduction (FH) =          1;
k-t BLAST =                     "no";
Overcontiguous slices =         "yes";
Stacks =                        1;
    slices =                    180;
    slice orientation =         "transverse";
    fold-over direction =       "RL";
    fat shift direction =       "P";
Stack Offc. AP (P=+mm) =        -3.0931561;
            RL (L=+mm) =        3.38424706;
            FH (H=+mm) =        18.5342007;
      Ang.  AP (deg) =          0.00924716238;
            RL (deg) =          -7.31103468;
            FH (deg) =          0.791477084;
      Free rotatable =          "no";
Multi-chunk =                   "no";
Large table movement =          "no";
PlanAlign =                     "no";
REST slabs =                    1;
    type =                      "free";
    orientation =               "transverse";
    thickness (mm) =            75.8213806;
Rest  Offc. AP (P=+mm) =        2.49528074;
            RL (L=+mm) =        8.45712852;
            FH (H=+mm) =        -120.044701;
      Ang.  AP (deg) =          -0.132635862;
            RL (deg) =          -4.93891001;
            FH (deg) =          1.81866467;
    power =                     "1";
Interactive positioning =       "no";
Patient position =              "head first";
        orientation =           "supine";
Scan type =                     "Imaging";
Scan mode =                     "3D";
    technique =                 "FFE";
Contrast enhancement =          "T1";
Acquisition mode =              "cartesian";
Fast Imaging mode =             "TFE";
    shot mode =                 "multishot";
TFE factor =                    112;
    startup echoes =            "default";
    shot interval =             "user defined";
        (ms) =                  3000;
    profile order =             "linear";
    turbo direction =           "Y";
Echoes =                        1;
    partial echo =              "no";
    shifted echo =              "no";
TE =                            "shortest";
Flip angle (deg) =              8;
TR =                            "user defined";
    (ms) =                      8.39999962;
Halfscan =                      "no";
Water-fat shift =               "user defined";
```

TCIN SEQUENCES DETAILS

```
     (pixels) =                 2.29999995;
Shim =                          "auto";
Fat suppression =               "no";
Water suppression =             "no";
TFE prepulse =                  "invert";
    slice selection =           "no";
    delay =                     "user defined";
        (ms) =                  1150;
    PSIR =                      "no";
MTC =                           "no";
T2prep =                        "no";
Diffusion mode =                "no";
SAR mode =                      "high";
B1 mode =                       "default";
PNS mode =                      "high";
Gradient mode =                 "default";
SofTone mode =                  "no";
Cardiac synchronization =       "no";
Respiratory compensation =      "no";
Navigator respiratory comp =    "no";
Flow compensation =             "no";
fMRI echo stabilisation =       "no";
NSA =                           1;
Angio / Contrast enh. =         "no";
Quantitative flow =             "no";
CENTRA =                        "no";
Manual start =                  "no";
Dynamic study =                 "no";
Preparation phases =            "auto";
Interactive F0 =                "no";
B0 field map =                  "no";
MIP/MPR =                       "no";
Images =                        "M", (3) "no";
Autoview image =                "M";
Calculated images =             (4) "no";
Reference tissue =              "Grey matter";
Recon compression =             "No";
Preset window contrast =        "soft";
Reconstruction mode =           "real time";
Save raw data =                 "no";
Hardcopy protocol =             "no";
Image filter =                  "system default";
Geometry correction =           "default";
Elliptical k-space shutter =    "default";
IF_info_seperator =             0;
Total scan duration =           "05:46.6";
Rel. SNR =                      0.999920011;
Act. TR/TE (ms) =               "8.4 / 3.9";
ACQ matrix M x P =              "256 x 256";
ACQ voxel MPS (mm) =            "0.90 / 0.90 / 1.80";
REC voxel MPS (mm) =            "0.90 / 0.90 / 0.90";
Scan percentage (%) =           100;
TFE shots =                     115;
TFE dur. shot / acq (ms) =      "1628.9 / 940.8";
Min. TI delay =                 518.618896;
Act. WFS (pix) / BW (Hz) =      "2.307 / 188.3";
Min. WFS (pix) / Max. BW (Hz) = "0.559 / 776.8";
Min. TR/TE (ms) =               "7.9 / 3.9";
SAR / head =                    "<  6 %";
Whole body / level =            "0.0 W/kg / normal";
SED =                           "  0.0 kJ/kg";
B1+rms =                        "0.56 uT";
Max B1+rms =                    "0.57 uT";
PNS / level =                   "57 % / normal";
dB/dt =                         "50.7 T/s";
Sound Pressure Level (dB) =     13.7661715;
```

TCIN fMRI sequence details

```
Coil selection 1 =              "SENSE-Head-32P";
     element selection =        "selection 1";
Coil selection 2 =              "SENSE-Head-32AH";
     element selection =        "selection 1";
Dual coil =                     "yes";
CLEAR =                         "yes";
    body tuned =                "no";
FOV          RL (mm) =          240;
             AP (mm) =          240;
             FH (mm) =          131.699997;
Voxel size   RL (mm) =          3;
             AP (mm) =          3;
Slice thickness (mm) =          3;
Recon voxel size (mm) =         3;
Fold-over suppression =         "no";
Reconstruction matrix =         80;
SENSE =                         "yes";
    P reduction (AP) =          2.5;
    P os factor =               1;
k-t BLAST =                     "no";
Stacks =                        1;
    type =                      "parallel";
    slices =                    40;
    slice gap =                 "user defined";
          gap (mm) =            0.299999952;
    slice orientation =         "transverse";
    fold-over direction =       "AP";
    fat shift direction =       "A";
Stack Offc. AP (P=+mm) =        -3.62547135;
            RL (L=+mm) =        -4.3553853;
            FH (H=+mm) =        38.6539917;
      Ang.  AP (deg) =          -0.0137504041;
            RL (deg) =          -7.96231651;
            FH (deg) =          -0.0233496893;
Minimum number of packages =    1;
Slice scan order =              "descend";
Large table movement =          "no";
PlanAlign =                     "no";
REST slabs =                    0;
Interactive positioning =       "no";
Patient position =              "head first";
        orientation =           "supine";
Scan type =                     "Imaging";
Scan mode =                     "MS";
    technique =                 "FFE";
Contrast enhancement =          "no";
Acquisition mode =              "cartesian";
Fast Imaging mode =             "EPI";
    shot mode =                 "single-shot";
Echoes =                        1;
    partial echo =              "no";
    shifted echo =              "no";
TE =                            "user defined";
    (ms) =                      25;
Flip angle (deg) =              90;
TR =                            "user defined";
    (ms) =                      2000;
Halfscan =                      "no";
Water-fat shift =               "user defined";
     (pixels) =                 11;
Shim =                          "auto";
Fat suppression =               "SPIR";
   strength =                   "strong";
   frequency offset =           "default";
Water suppression =             "no";
MTC =                           "no";
Diffusion mode =                "no";
SAR mode =                      "high";
B1 mode =                       "default";
```

```
PNS mode =                      "high";
Gradient mode =                 "maximum";
SofTone mode =                  "no";
Cardiac synchronization =       "no";
Respiratory compensation =      "no";
Navigator respiratory comp =    "no";
Flow compensation =             "no";
Temporal slice spacing =        "minimal";
fMRI echo stabilisation =       "no";
NSA =                           1;
Angio / Contrast enh. =         "no";
Quantitative flow =             "no";
Manual start =                  "yes";
Dynamic study =                 "individual";
    dyn scans =                 417;
    dyn scan times =            "shortest";
    FOV time mode =             "default";
    dummy scans =               0;
    immediate subtraction =     "no";
    fast next scan =            "no";
    synch. ext. device =        "yes";
        start at dyn. =         1;
        interval (dyn) =        1;
    dyn stabilization =         "yes";
    prospect. motion corr. =    "no";
Keyhole =                       "no";
Arterial Spin labeling =        "no";
Preparation phases =            "full";
Interactive F0 =                "no";
B0 field map =                  "no";
MIP/MPR =                       "no";
Images =                        " M", (3) " no";
Autoview image =                " M";
Calculated images =             (4) " no";
Reference tissue =              "Grey matter";
Preset window contrast =        "soft";
Reconstruction mode =           "real time";
Save raw data =                 "no";
Hardcopy protocol =             "no";
Ringing filtering =             "default";
Geometry correction =           "default";
IF_info_seperator =             0;
Total scan duration =           "14:00.0";
Rel. signal level (%) =         100;
Act. TR/TE (ms) =               "2000 / 25";
Dyn. scan time =                "00:02.0";
Time to k0 =                    "0.994";
ACQ matrix M x P =              "80 x 79";
ACQ voxel MPS (mm) =            "3.00 / 3.00 / 3.00";
REC voxel MPS (mm) =            "3.00 / 3.00 / 3.00";
Scan percentage (%) =           100;
Packages =                      1;
Min. slice gap (mm) =           0;
EPI factor =                    35;
Act. WFS (pix) / BW (Hz) =      "10.999 / 39.5";
BW in EPI freq. dir. (Hz) =     "1848.6";
Min. WFS (pix) / Max. BW (Hz) = "6.516 / 66.7";
Min. TR/TE (ms) =               "1955 / 8.8";
SAR / head =                    "<  39 %";
Whole body / level =            "< 0.1 W/kg / normal";
B1 rms =                        "1.46 uT";
PNS / level =                   "94 % / 1st level";
Sound Pressure Level (dB) =     20.6506329;
```

TCIN diffusion sequence details

```
SmartSelect =                    "yes";
Coil 1  (exclude) =              "None";
Uniformity =                     "CLEAR";
FOV          RL (mm) =           256;
             AP (mm) =           256;
             FH (mm) =           130;
Voxel size   RL (mm) =           2;
             AP (mm) =           2;
Slice thickness (mm) =           2;
Recon voxel size (mm) =          2;
Fold-over suppression =          "no";
Reconstruction matrix =          128;
SENSE =                          "yes";
    P reduction (AP) =           2.20000005;
k-t BLAST =                      "no";
Stacks =                         1;
    type =                       "parallel";
    slices =                     65;
    slice gap =                  "user defined";
          gap (mm) =             0;
    slice orientation =          "transverse";
    fold-over direction =        "AP";
    fat shift direction =        "P";
Stack Offc. AP (P=+mm) =         -7.80269909;
            RL (L=+mm) =         -6.29022074;
            FH (H=+mm) =         23.5311985;
      Ang.  AP (deg) =           0.317858964;
            RL (deg) =           -11.9173689;
            FH (deg) =           -2.05776381;
      Free rotatable =           "no";
Minimum number of packages =     1;
Slice scan order =               "default";
Large table movement =           "no";
PlanAlign =                      "no";
REST slabs =                     0;
Interactive positioning =        "no";
Patient position =               "head first";
        orientation =            "supine";
Scan type =                      "Imaging";
Scan mode =                      "MS";
    technique =                  "SE";
Modified SE =                    "no";
Acquisition mode =               "cartesian";
Fast Imaging mode =              "EPI";
    shot mode =                  "single-shot";
Echoes =                         1;
    partial echo =               "no";
TE =                             "user defined";
    (ms) =                       73;
Flip angle (deg) =               90;
TR =                             "user defined";
    (ms) =                       12312;
Halfscan =                       "yes";
    factor =                     0.779661;
Water-fat shift =                "user defined";
     (pixels) =                  27;
Shim =                           "auto";
mDIXON =                         "no";
Fat suppression =                "SPIR";
   strength =                    "strong";
   frequency offset =            "user defined";
      offset (Hz) =              250;
Grad Rev Fat suppression =       "no";
Water suppression =              "no";
BB pulse =                       "no";
MTC =                            "no";
Diffusion mode =                 "DTI";
    gradient overplus =          "no";
    directional resolution =     "from file";
```

```
    average high b =            "user defined";
        b-factor averages =     "(0) 4",
                                "(1500) 1", "", "", "", "",
                                "", "", "", "", "", "", "",
                                "", "", "", "", "", "", "",
                                "", "", "", "", "", "", "",
                                "", "", "", "", "";
SAR mode =                      "high";
B1 mode =                       "default";
PNS mode =                      "high";
Gradient mode =                 "enhanced";
SofTone mode =                  "no";
Cardiac synchronization =       "no";
Respiratory compensation =      "no";
Navigator respiratory comp =    "no";
Flow compensation =             "no";
Temporal slice spacing =        "default";
NSA =                           1;
Manual start =                  "no";
Dynamic study =                 "no";
    dyn stabilization =         "regular";
Preparation phases =            "auto";
Interactive F0 =                "no";
B0 field map =                  "no";
MIP/MPR =                       "no";
Images =                        "M", (3) "no";
Autoview image =                "M";
Calculated images =             (4) "no";
Reference tissue =              "White matter";
Recon compression =             "No";
Preset window contrast =        "soft";
Reconstruction mode =           "immediate";
Save raw data =                 "no";
Hardcopy protocol =             "no";
Image filter =                  "system default";
Geometry correction =           "default";
IF_info_seperator =             1634755923;
Total scan duration =           "15:38.2";
Rel. SNR =                      1;
Act. TR (ms) =                  "12312";
Act. TE (ms) =                  "73";
ACQ matrix M x P =              "128 x 128";
ACQ voxel MPS (mm) =            "2.00 / 2.00 / 2.00";
REC voxel MPS (mm) =            "2.00 / 2.00 / 2.00";
Scan percentage (%) =           100;
Packages =                      1;
Min. slice gap (mm) =           -0;
User defined DTI scheme =
                                "Dti61b1500_p (62, 1500)";
EPI factor =                    59;
WFS (pix) / BW (Hz) =           "23.149 / 18.8";
BW in EPI freq. dir. (Hz) =     "1907.4";
Min. TR (ms) =                  "7483";
SPIR offset act./default (Hz) = "250 [220]";
SAR / head =                    "<  19 %";
Whole body / level =            "0.0 W/kg / normal";
SED =                           "  0.0 kJ/kg";
B1+rms =                        "1.03 uT";
Max B1+rms =                    "1.03 uT";
PNS / level =                   "70 % / normal";
dB/dt =                         "54.3 T/s";
Sound Pressure Level (dB) =     13.7679567;
```

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