FUNCTIONAL AND STRUCTURAL NEUROPLASTICITY IN DEPRESSION

FUNCTIONAL AND STRUCTURAL NEUROPLASTICITY IN MAJOR DEPRESSIVE DISORDER

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LAY ABSTRACT

The characterization of brain changes in Major Depressive Disorder (MDD) has resulted in contradictory findings, and gaps in understanding how the brain changes in response to antidepressant treatment. This dissertation aims to characterize brain changes in MDD through a series of neuroimaging studies. Chapter 1 provides an introduction to MDD and brain changes in MDD. Chapter 2 presents an examination of memory in treatment naïve patients with MDD. Chapter 3 presents a study of acute tryptophan depletion in midlife women receiving estrogen-based treatment on an emotional conflict task. Chapter 4 examines unmedicated patients with MDD and healthy control participants on an emotional conflict task. Chapter 5 examines the effects of antidepressant treatment on performance on an emotional conflict task. Chapter 6 presents a case study of a patient with ventriculomegaly with mood and cognitive impairments. Chapter 7 summarizes the contributions of this research and discusses implications and future directions.

ABSTRACT

The brain has the capacity to modify itself structurally and functionally, to adapt to novel circumstances. Adaptive changes in neural circuitry that become intransigent, such as continued hypervigilance after resolution of a threat situation, become maladaptive and may facilitate development of psychiatric disorders such as Major Depressive Disorder (MDD). Although MDD pathogenesis is unclear, hypothalamic-pituitary-adrenal axis dysregulation may facilitate the neuroplastic changes observed in MDD. Whether these neuroplastic changes facilitate the development of MDD or develop due to MDD remains unclear. The characterization of neuroplastic changes in MDD has resulted in sometimes contradictory findings. There are gaps in understanding the timing of neuroplastic changes in MDD, and how and when they are affected by antidepressant treatment. Characterization of neuroplasticity in MDD may uncover different phenotypes and aid in the discovery of a predictive biomarker of antidepressant treatment response. This dissertation presents the results of a series of neuroimaging studies. Chapter 1 provides an introduction to neuroplasticity and MDD. In Chapter 2 results of a study examining hippocampal memory function in treatment naïve patients with MDD are presented. Chapter 3 exhibits findings from a study examining effects of an acute tryptophan depletion paradigm in midlife women receiving estrogen-based treatment on an emotional conflict task. Chapter 4 discusses results from an examination of unmedicated patients with

MDD and healthy control participants on an emotional conflict task. Chapter 5 presents longitudinal data of the sample from Chapter 4, and the effect of 8 weeks of treatment with antidepressant escitalopram on performance on an emotional conflict task. In Chapter 6 a case study is presented of a patient with long-standing overt ventriculomegaly, whose chief complaint was of mood and cognitive impairments. Chapter 7 summarizes the findings and contributions of this body of research and discusses clinical implications and future directions.

EPIGRAPH

"The brain is a living mechanism, not a machine. In case of breakdown, it can substitute one of its parts for the function of another. But it has its limitations. It is subject to inexorable change with the passage of time."

– Wilder Penfield (1953).

"Every man can, if he so desires, become the sculptor of his own brain."

– Santiago Ramon y Cajal (1955)

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PREFACE

The work presented in Chapter 2 has been published as Alders GL, Milne AMB, Minuzzi L, Frey BN, MacQueen GM, & Hall GB. (2019). Altered hippocampal function with preserved cognitive performance in treatment-naive major depressive disorder. *Neuroreport, 30*(1), 46-52. The data for this study was collected by Andrea Milne at McMaster University, and neuroimaging analyses were also completed by Andrea Milne. I completed the behavioural data analyses and wrote the manuscript for the published paper.

The work presented in Chapter 3 has been submitted for publication as Alders GL, Minuzzi L, Hall GB, Mahoney JL, Fedorkow D, Costescu-Green D, Skelin I, Frey BN, Steiner M, Soares CN. (2019). Differential effects of acute tryptophan depletion on emotional Stroop in midlife women receiving estrogen-based treatment: an fMRI study. (Submitted to *Menopause*). Data for this study was collected by Julie Mahoney and Kimberly Vogt at McMaster University. I completed neuroimaging and behavioural and demographic data analyses and wrote the manuscript, which has been submitted to the journal Menopause.

The work presented in Chapter 4 has been published as Alders GL, Davis AD, MacQueen G, Strother SC, Hassel S, Zamyadi M, Sharma GB, Arnott SR, Downar J, Harris JK, Lam RW, Milev R, Müller DJ, Ravindran A, Kennedy SH, Frey BN, Minuzzi L, Hall GB, on behalf of the CAN-BIND Investigator Team. (2019). Reduced accuracy accompanied by reduced neural activity during the

performance of an emotional conflict task by unmedicated patients with major depression: A CAN-BIND report. *Journal of Affective Disorders*, *257*, (765-773).

The work presented in Chapter 5 has been submitted for publication as Alders GL, Davis AD, MacQueen G, Strother SC, Hassel S, Zamyadi M, Sharma GB, Arnott SR, Downar J, Harris JK, Lam RW, Milev R, Müller DJ, Ravindran A, Kennedy SH, Frey BN, Minuzzi L, Hall GB, on behalf of the CAN-BIND Investigator Team. (2019). Escitalopram ameliorates differences in neural activity between healthy comparison and major depressive disorder groups on an fMRI emotional conflict task: A CAN-BIND report. (Submitted to *Journal of Affective Disorders*).

The data for the studies presented in Chapters 4 and 5 were collected as part of the Canadian Biomarker Integration Network in Depression (CAN-BIND), which I joined as a trainee after data collection had begun. I wrote the publication proposals for papers presented in Chapters 4 and 5, to request access to the multi-site CAN-BIND study data. I conducted the MRI sessions, and collected and uploaded neuroimaging and behavioural data for participants recruited to the CAN-BIND study at the McMaster University study site. Neuroimaging data pre-processing was completed off-site, according to CAN-BIND protocol. Andrew Davis was instrumental in assisting with pre-processing of the behavioural data, and Andrew and I worked together on the scripts for processing of neuroimaging data. I completed statistical analyses of demographic, behavioural, and neuroimaging data presented in these chapters. I composed the manuscript that

has been published for the work presented in Chapter 4, and the manuscript which has been submitted for the work presented in Chapter 5.

The work presented in Chapter 6 has been published as Alders GL, Minuzzi L, Sarin S, Frey BN , Hall GB , & Samaan Z. (2018). Volumetric MRI analysis of a case of severe ventriculomegaly. *Frontiers in Human Neuroscience*, 12:1-5. I completed the manual segmentation for the patient presented in the case study, and calculated the gray matter, white matter, and cerebrospinal fluid volumes for the control participants. Dr. Luciano Minnuzi calculated the gray matter, white matter, and cerebrospinal fluid volumes for the case study participant, based on the manual segmentation information that I provided. An early outline of the introduction and methods/results was written by Dr. Sachin Sarin. I wrote a revision of the introduction altering the framework and justification for the case study. I wrote a revised methods/results section to include additional demographic and assessment information and manual segmentation results, and the discussion for the work which has been published.

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List of Abbreviations

4D – 4 dimensional

$5HT_{1A}$ – presynaptic serotonin autoreceptor 1A

$5HT_{2A}$ – post-synaptic serotonin autoreceptor 2A

ACC – anterior cingulate cortex

ATD – acute tryptophan depletion

B_0 – an externally applied constant and homogeneous magnetic field

BA – Brodmann area

BDI – Beck Depression Inventory

BDNF – brain-derived neurotrophic factor

BOLD – blood oxygen level dependent

CA – cornu ammonis

CAN-BIND – Canadian Biomarker Integration Network in Depression

CAN-BIND-1 – Canadian Biomarker Integration Network in Depression

CANMAT – Canadian Network for Mood and Anxiety Treatments

cC – a congruent trial preceded by a congruent trial (refers to the Emotional Conflict Task)

cI – an incongruent trial preceded by a congruent trial (refers to the Emotional Conflict Task)

CNS-VS – CNS-Vital Signs

dACC – dorsal anterior cingulate cortex

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth edition

DSM-V – Diagnostic and Statistical Manual of Mental Disorders, fifth edition

ECT – Emotional Conflict Task

ET – estrogen treatment

FDR – false discovery rate

FLAIR – fluid-attenuated inversion recovery

fMRI – functional Magnetic Resonance Imaging

FOV – field of view

FWHM – full width half maximum

GCS – Greene Climacteric Scale

GLM – general linear model

H_20 – water (hydrogen dioxide)

HC – healthy comparison participant

HFRDIS – Hot Flash Related Daily Interference Scale

HT – hormone therapy

HPA – hypothalamic-pituitary-adrenal

iC – an incongruent trial preceded by a congruent trial (refers to the Emotional Conflict Task)

iI – an incongruent trial preceded by an incongruent trial (refers to the Emotional Conflict Task)

IQ – intelligence quotient

iSPOT-D – International Study to Predict Optimized Treatment in Depression

MADRS – Montgomery–Åsberg Depression Rating Scale

MAO – monoamine oxidase

MDD – Major Depressive Disorder

MDD-8 – MDD patients that reached remitter definition at week 8

MDD-16 – MDD patients that reached remitter definition at week 16

MDD-NR – MDD patients that did not meet remitter definition at weeks 8 or 16 and are therefore classified as non-remitters

MDE – major depressive episode

MHz – megahertz

MINI – Mini-International Neuropsychiatric Interview

MNI – Montreal Neurological Institute

MOTCOR – motion correction

MPEs – motion parameter estimates

MRI – magnetic resonance imaging

MR – magnetic resonance

NAMS – North American Menopause Society

NMDA – N-methyl-D-aspartate

PC – principal components

PCA – principal component analysis

POMS – Profile of Mood Scales

RDoC – National Institute of Mental Health's Research Domain Criteria initiative

REB – research ethics board

RF – radio frequency

ROI – region of interest

RT – reaction time

SNRI – serotonin and noradrenaline reuptake inhibitors

SSRI – selective serotonin reuptake inhibitors

STRAW – Stages of Reproductive Aging Workshop

T – Tesla

TCA – tricyclic antidepressants

TCPS – Tri-Council Policy Statement

TE – time to echo

TR – time to repetition

USD – United States Dollars

WAIS-III – Wechsler Adult Intelligence Scale – 3rd Edition

Chapter 1

Introduction

With the advent of advanced neuroimaging techniques, such as magnetic resonance imaging (MRI) it has become possible to quantify and qualify macroscopic neuroplastic changes in the brain. For the purposes of this dissertation, neuroplasticity is defined as the neural capacity for synaptic reorganization in response to new information, changing circumstances or experiences, an insult, (Ruiz et al., 2018) or physiological stress. The aim of this body of work is to broaden our current understanding of neuroplastic changes in patients with depression.

Depression is the greatest contributor to the number of years lived with a disability (7.5%), and affects about 4.4% of the global population, which translates to about 322 million persons world-wide, and 48.6 million persons in the region of the Americas specifically (World Health Organization, 2017). In addition to this, depression also contributes to burden of ischemic heart disease and suicide (Ferrari et al., 2013).

DSM-V Characterization of MDD

The depressive disorders described in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) (American Psychiatric Association, 2014) are characterized by either an irritable mood, a feeling of emptiness, or a

sad mood, along with alterations in cognition and somatic changes that interfere with the an individual's competence and ability to complete activities of daily living. These different diagnoses exist along a continuum and can be differentiated from one another by means of assumed etiology, the time in life the disorder occurs, and the duration of the experience (American Psychiatric Association, 2014). The DSM-V (American Psychiatric Association, 2014) diagnostic criteria for MDD require a change from a preceding level of functioning to a situation in which the person experiences at least 5 of the following symptoms throughout the identical period of 2 weeks, one of which must be either a depressed mood nearly every day for the better part of the day, or feelings of anhedonia/a loss of pleasure or interest in most or all activities nearly every day for the better part of the day, and at least 4 of the following: repetitive suicidal ideation with or without a specific plan, or a suicide attempt, or incessant thoughts about death, either significant weight gain or weight loss if not following a diet, or an increased or diminished appetite almost every day, hypersomnia or insomnia almost every day, feelings of inappropriate or disproportionate guilt, or feelings of worthlessness on an almost daily basis, a psychomotor reduction or agitation on an almost daily basis, feelings of low energy or fatigue on most days, or indecisiveness, or reduced competence to concentrate or think almost every day. In addition to this, these symptoms interfere with activities of daily living including socially or occupationally, or these activities require a significantly greater effort to execute than usual, and the episode is not due to a medical

infirmity, or to a medication/substance. Taken together, these criteria comprise a major depressive episode (MDE). Further, a MDE must be the best explanation for the current situation after ruling out other types of mood disorders including disorders on the spectrum of schizophrenia, delusional disorders or psychotic disorders, and there has never been a hypomanic/manic episode (American Psychiatric Association, 2013).

Depression Prevalence

World-wide, there are sex differences in depression prevalence. Prevalence is higher in females (5.1%) compared to males (3.6%) (World Health Organization, 2017). In the 2012 Canadian population, across age groups between 15 and 64 years, prevalence was higher in females (5.8%), than in males (3.6%), with rates between the sexes becoming comparable at age 65 and older (Pearson et al., 2013). The Canadian lifetime prevalence rate for depression is 11.2%, with females at twice the lifetime risk of developing MDD, compared to males (Odds Ratio (OR) = 1.8) (Knoll & MacLennan, 2017). Prior to puberty, females may be similarly or less prone to developing depression, than males (Cyranowski et al., 2000). A disproportionate prevalence of depression between males and females first emerges after menarche (Weller et al., 2006) between the ages of 11 and 13 (Cyranowski et al., 2000) and diminishes subsequent to menopause (Pearson et al., 2013). However, a recent epidemiological study suggests that the sex difference in MDD prevalence persists beyond the age of 60 years (Girgus et al., 2017).

Greater Prevalence of Depression in Women

Socioeconomic risk factors for MDD include having less education, less material resources, female sex, unemployment, or being widowed/divorced (Rai et al., 2013). A number of socioeconomic factors have been associated with increased vulnerability for depression in females including poverty (Simmons et al., 2008), greater exposure to childhood sexual abuse, violence against women and girls, and gender discrimination (Kuehner, 2017).

The increased propensity for women to develop a mood disorder may be associated, in part, with periods of fluctuation in gonadal hormones across the lifespan, sometimes referred to as windows of vulnerability (Soares & Zitek, 2008; Steiner, 2003). Fluctuations in the hormonal milieu during the reproductive years may occur in the menstrual cycle in the luteal phase (Hantsoo & Epperson, 2015), as well as postpartum (Marcus, 2009), and in the transition to menopause (Bromberger & Epperson, 2018).

Considering the menopausal transition, risk for experiencing depression is lower prior to menopause and increases in perimenopause and early postmenopause (Bromberger et al., 2011; Cohen et al., 2006). Women with no lifetime history of MDD have a 28% greater risk of developing depression during the menopause transition, while this risk is almost doubled (59%) in women with a lifetime history of MDD (Bromberger et al., 2015). Risk is also increased in women with a past history of severe premenstrual mood symptoms or who are experiencing hot flashes, or poor sleep in perimenopause (Freeman et al., 2004).

Nevertheless, it is likely that these fluctuations are not the sole cause of mood disorders or premenstrual syndromes (Rubinow et al., 1988). A more likely explanation is that a subset of females is more vulnerable to natural fluctuations in the sex hormone milieu (Bloch et al., 2000; Freeman et al., 2004; Frey & Soares, 2009) or that they experience more extreme variability in the these fluctuations around a woman's own average range (Freeman et al., 2006).

Establishing a Diagnosis of MDD

An MDD diagnosis takes into account whether the patient is experiencing a single or recurrent MDE, how severe the MDE is (as determined by number of symptoms in addition to the minimum 5), whether or not there are features of psychosis, and the remission status (remission defined as ≥ 2 consecutive months between different episodes in which the patient does not reach the criteria for an MDE) (American Psychiatric Association, 2013).

Depression Course

MDD emergence, phenomenology and treatment response, does not differ by sex (American Psychiatric Association, 2014). Risk of onset is greatly increased at the time of puberty, and children with MDD may present with irritability rather than sadness (American Psychiatric Association, 2014). With respect to treatment response, pediatric samples benefit from treatment with selective serotonin reuptake inhibitors (SSRI) over placebo and greatest response is observed early in the treatment course, although pediatric populations experience a diminished benefit in response to SSRI as compared to adult patients with MDD (Varigonda

et al., 2015; Vitiello & Ordonez, 2016). In addition to this, pediatric populations appear to respond best to SSRI fluoxetine (Cipriani et al., 2016; Vitiello & Ordonez, 2016).

The natural course of MDD varies. Up to half of patients will experience a brief MDE (Lam et al., 2016a) with a median recovery rate of 3 months, with up to 20% of patients experiencing an MDE duration of ≥2 years (Eaton et al., 1997; Spijker et al., 2002).

Remission is defined as ≥2 months with either no symptoms or up to two symptoms mild in severity (American Psychiatric Association, 2013). Compared to patients that achieve full remission, partially remitting patients have an increased likelihood of MDE recurrence or relapse, as do patients with residual mild symptoms (Paykel, 2008; Paykel et al., 1995).

Cognitive Impairment in Depression

The majority of treatments for MDD address mood symptoms, while failing to adequately target impairments in higher order cognitive function, which may contribute to the failure to reach full remission in some patients (Shilyansky et al., 2016; Zuckerman et al., 2018). Cognitive impairment often persists beyond amelioration of mood symptoms (Hammar & Ardal, 2009; Hasselbalch et al., 2011; Ladegaard et al., 2016; Rock et al., 2014). Improvements in cognition may play an important role in helping patients reach full remission (Harmer & Cowen, 2013; Harmer et al., 2017; Jaeger et al., 2006). A negative bias in processing information in MDD related to regular social and emotional situations and

interactions (Bouhuys et al., 1999; Bourke et al., 2010; Gotlib et al., 2011; Stuhrmann et al., 2011) may contribute to the development of depressive symptomatology (Gotlib & Joormann, 2010; Harmer et al., 2017). This negative bias may serve to maintain negative cognitions associated with depression such as the tendency to focus on negative information or the tendency to recall less positive information about the self (Gotlib & Joormann, 2010; Roiser & Sahakian, 2013). Some research suggests that analysis of neural responding to processing of negative stimuli may be helpful in identifying individuals in whom this may indicate a vulnerability for developing depression or indicating which patients with MDD may respond best to a selected treatment (Roiser & Sahakian, 2013). Some reports suggest that improvements in emotional information processing facilitate improvements in mood in MDD (Harmer & Cowen, 2013; Tranter et al., 2009). Thus, residual, or persistent cognitive impairment may be a contributing factor for future relapse (Inoue et al., 2006; Maeshima et al., 2016).

Cognitive impairments experienced during an acute MDE may include impairments of attention and concentration (Rock et al., 2014; Shilyansky et al., 2016), memory (Dillon & Pizzagalli, 2018; Hickie et al., 2005; Rock et al., 2014; Shilyansky et al., 2016), psychomotor speed (Bennabi et al., 2013), executive functioning (Rock et al., 2014; Shilyansky et al., 2016), and social cognition (Ladegaard et al., 2016) including emotion recognition (Dalili et al., 2015).

Given the clinical implications of association between psychosocial functioning and higher-order cognitive functioning in MDD (Hammar & Ardal,

2009; Jaeger et al., 2006; Lam et al., 2014) identifying, quantifying, and minimizing cognitive deficits may play an important role in assisting patients on the path to remission (McIntyre & Lee, 2016; Rock et al., 2014) and the road to regaining premorbid levels of functioning (Kennedy, 2002).

Depression and Comorbidity

MDD is often a comorbidity of chronic illness, diminishing health-related quality of life (Egede & Hernández-Tejada, 2013; Ishak et al., 2014; Raab et al., 2015). Depression increases risk for a number of serious chronic diseases including diabetes, cancer, stroke, and heart disease (Voinov et al., 2013), and may be considered a mortality risk factor on par with smoking (Mykletun et al., 2009).

Socioeconomic Factors, Health-Related Quality of Life, and Depression

Patients with depression also experience lower income, diminished level of functioning in relationships and social interactions, and impaired capacity to perform at work (Kessler, 2012; Scheele et al., 2013). Finally, and not least importantly, there is a significant reduction in health-related quality of life in patients with MDD, which is independently associated with both depressive symptom severity, level of functioning/disability, age, and degree of cognitive impairment, even up to two years post treatment initiation or treatment alterations (Ishak et al., 2013; Saragoussi et al., 2018).

Depression Remission and Recurrence

A cure for MDD remains elusive. Treatments currently available may help to alleviate symptom severity while an MDE runs its course, and to prevent

recurrence (Geddes et al., 2003). The mean response to placebo in trials of antidepressants is in the range of 35-40% (Furukawa et al., 2016; Furukawa et al., 2018), and may stem at least in part, from spontaneous remission rates (Cipriani et al., 2018). However, antidepressant treatment is still more effective than treatment with placebo (Cipriani et al., 2018). Remission to interventions with SNRI or SSRI antidepressants is in the range of 56-71% (Novick et al., 2017).

MDD is episodic in nature (Solomon et al., 2000). A population-based prospective cohort with a follow up period of 23 study found that 50% of patients recovered and did not experience another MDE during the study observation period, 35% experienced recurrent MDD and 15% of patients unremitting MDD (Eaton et al., 2008). Across the lifespan, patients with recurrent MDD may experience between five (Kessler & Walters, 1998) and nine (Kessler et al., 1997) MDEs.

Treatment Resistant Depression

In Canada, prevalence of treatment resistant depression in primary care, defined as non-response to two antidepressant treatments from different classes, is 21.7%, and does not differ across sexes (Rizvi et al., 2014). The indirect and direct costs of treatment resistant depression are estimated to be 50% greater than for patients that respond to antidepressant treatment, perhaps in part due to longer episode duration, or increased number of treatment steps required for this patient group to find a treatment that will provide symptom relief (Ivanova et al., 2010).

CANMAT Depression Treatment Guidelines

The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for treatment of MDD in adults recommends treatments for mild depression include psychological education, psychological therapy, and self-management (Kennedy et al., 2016). Recommendations for patients with moderate to severe MDD include SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), monoamine oxidase (MAO) inhibitors, melatonin receptor agonists, α-adrenergic agonists, and serotonin receptor agonists and antagonists, noradrenaline and dopamine reuptake inhibitors, to name a few, as well as options for adjunctive treatment (Kennedy et al., 2016). In addition, psychological treatments including behavioural activation, interpersonal therapy or cognitive behavioural therapy, or mindfulness-based cognitive therapy, or combined cognitive behavioural therapy and interpersonal therapy with pharmacotherapy may also be options (Kennedy et al., 2016). Neurostimulation treatment options are recommended for patients with treatment-resistant MDD and include transcranial direct current stimulation as a first line recommendation, and second line recommendation of electroconvulsive therapy (Milev et al., 2016).

A criticism of current pharmacotherapy options for MDD is that subjective changes in symptom severity are often not experienced until ≥ 2 weeks after treatment begin (Kennedy et al., 2016; Liu et al., 2017). Current guidelines indicate that early improvements measured within the first 2 to 4 weeks of

treatment begin correlate with response/remission at 6 to 12 weeks, suggesting an extended period of time for antidepressant medications to reach their full treatment potential (Kennedy et al., 2016). Maintaining this treatment regimen through remission into a maintenance cycle reduces the risk for relapse, but in some patients experiencing recurrent MDEs, antidepressant treatment may become increasingly less effective (Kaymaz et al., 2008).

CANMAT recommendations for women experiencing perimenopausal depression include first line recommendations of SNRI (desvenlafaxine) or cognitive behavioural therapy, and second line recommendations of transdermal estradiol (with concomitant progesterone for women with intact uterus), or SSRI (citalopram or escitalopram), SNRI (duloxetine or venlafaxine XR), or noradrenergic and specific serotonergic antidepressant (mirtazapine), or atypical antipsychotic (quetiapine XR) (MacQueen et al., 2016).

More recently, the North American Menopause Society (NAMS) recommendation for women experiencing an MDE in perimenopause suggests prescribing of proven first line treatments including CBT or other psychotherapy options or antidepressant medication including SSRI and SNRI options (Maki et al., 2018). From a treatment efficacy perspective, NAMS guidelines report that only SNRI desvenlafaxine has been examined in a placebo-controlled large randomized trial of perimenopausal and postmenopausal women. NAMS does not recommend estrogen treatment for mood disorders in perimenopause or postmenopause.

Social and Economic Burden of Depression

Depression places a significant burden on both the healthcare system, patients, their caregivers, and the economy, accounting for 33% of total cost for brain disorders in Europe which corresponds to 1% of gross domestic product for the entire European economy (Sobocki et al., 2006). The excess healthcare costs associated with Major Depressive Disorder (MDD) in Ontario, Canada, at a conservative estimate is $709 per capita (excluding costs associated with drugs, emergency department visits, laboratory tests, or non-physician or hospital-based services) (Chiu et al., 2017). There are also significant economic burdens attached to employee absences, presenteeism, and lost productivity at work (Chow et al., 2019; Stewart et al., 2003).

Treatment Response Biomarkers in Depression

A reliable biomarker for predicting treatment response in MDD remains elusive. Studies have examined the possibility of finding a treatment response prediction algorithm with the help of machine learning incorporating genetic, demographic and symptom severity information (Lin et al., 2018) or incorporating neuroimaging information (Gao et al., 2018). The Canadian Biomarker Integration Network in Depression (CAN-BIND) is a research consortium that is hoping to find indicators or predictors for MDD treatment response by examining a combination of molecular, genetic, cognitive, demographic, social, and neuroimaging information (www.canbind.ca; Lam et al., 2016b). Chapters 4 and 5 refer to data collected as part of the CAN-BIND initiative.

Magnetic Resonance Imaging for Identifying Neuroplasticity in MDD

MRI is a non-invasive method of imaging that produces three dimensional images of the brain, that are useful for imaging functional and structural neuroplasticity in the brain. The brain and spinal cord are made of 73% water (H_20) (Mitchell et al., 1945), and MRI exploits the magnetic properties of the hydrogen atoms that comprise water. Hydrogen protons possess spin, a quantum mechanical property, that can be oriented in different directions and is akin to a small rotating magnet, similar to the earth rotating on its axis, with a north and a south pole (Berger, 2002; Logothetis, 2008). When an externally applied magnetic field (B_0) is brought to bear on the usually randomly oriented spins, such as when the body is moved into an MRI scanner, the spins, like the wobbling motion of a spinning top, will wobble or precess longitudinally around the magnetic field's axis (Berger, 2002; Logothetis, 2008). As more energy is required to align antiparallel to the externally applied magnetic field, compared to aligning parallel to the magnetic field, overall there is a summed excess of spins in parallel alignment with the magnetic field, and this summed system of spins results in a magnetization vector (Berger, 2002; Logothetis, 2008). However, magnetic resonance due to the difference in parallel and antiparallel alignment is low at 1.5 Tesla (about one in 10,000,000) (Logothetis, 2008). The Larmor frequency is the rate at which spins precess, and is expressed as $\omega = \gamma B_0$ where precession frequency is determined by the gyromagnetic ratio or how quickly the proton is spinning (expressed in MHz), multiplied by the strength of the magnetic field by (expressed in Tesla)

(Logothetis, 2008). At 3 Tesla, the Larmor frequency for hydrogen is 127.74 MHz Magnetic resonance occurs when a magnetization vector is exposed to a radiofrequency (RF) pulse (B_1) created by sending alternating current through an RF coil (Elster, 2018b) at or near the Larmor frequency, causing the magnetization vector to deviate from its previous position at magnetization equilibrium, by 90 degrees, into the transverse plane (Logothetis, 2008). A radiofrequency receiver coil can then detect the magnetization emitted while the magnetization vector is in the transverse plane (Logothetis, 2008). After the RF pulse, protons return to their orientation along the magnetization vector of B_0, a process called relaxation, and as they do so the signal released decays as they return to realign with B_0 (Berger, 2002; Logothetis, 2008). Depending on the type of matter (grey matter, white matter, CSF or blood vessels), relaxation rates differ, and the differences in these relaxation rates form the foundation for constructing image contrast (Logothetis, 2008).

When activity in a region of the brain increases, the regional cerebral blood flowing through that region increases, as does glucose utilization, to restore oxygen that has been consumed due to cell activity, and this change in the ratio of oxygenated to deoxygenated blood concentration is called the blood oxygen level dependent (BOLD) signal (Logothetis, 2008; Poldrack et al., 2012). Task-based functional MRI (fMRI) is reliant on the hemoglobin in the red blood cells. Deoxygenated blood is paramagnetic and emits a quantifiable additive magnetic field, with four of six outer electrons being unpaired, the iron is in a high spin

state (Logothetis, 2008). Conversely, in oxygenated blood the heme iron receives the electrons from the oxygen and is thus in a low-spin state and is diamagnetic, which means that it weakly deflects the magnetic field that has been applied (Logothetis, 2008). In response to neural activity, regional cerebral blood flow increases, supplying more oxygenated blood than the metabolic oxygen consumption rate requires (Elster, 2018a; Fox & Raichle, 1986). This results in an overabundance of oxygenated blood, increasing the ratio of oxygenated to deoxygenated blood, and increased BOLD signal in response to neural activity (Elster, 2018a; Fox & Raichle, 1986). Thus, the BOLD signal is dependent on a combination of cerebral blood volume, cerebral blood flow, and cerebral metabolic rate of oxygen (Jorge et al., 2018; Logothetis, 2003). Neural activation in response to task-based paradigms is most often observed as a positive BOLD response (Jorge et al., 2018).

Task-based fMRI measures neural activity on a macroscopic level, and corresponds to activity changes in neuronal populations that are correlated with local field potentials, which suggests that activity detected is a combination of input that is arriving and being processed locally, as opposed to measuring spiking activity (Logothetis, 2003). Thus, the BOLD activity will likely correlate with pre- and postsynaptic currents and release of neurotransmitters and less with single unit activity (Logothetis, 2003). The advent of task-based fMRI has allowed the examination of localized functional neuroplasticity and how it may

change as a function of disease progression and in response to antidepressant treatment.

Diagnostic Biomarkers for Depression

As yet no biomarker has been discovered that has sufficient specificity or sensitivity to be used to determine a definitive diagnosis of MDD, in spite of wide-ranging research describing physiological features and symptoms associated with this diagnosis (American Psychiatric Association, 2013). In the current context, a biomarker may be defined as "a biological observation that substitutes for and ideally predicts a clinically relevant endpoint or intermediate outcome that is more difficult to observe" and "should be measurable with little or no variability, should have a sizeable signal to noise ratio, and should change promptly and reliably in response to changes in the condition or its therapy" (Aronson & Ferner, 2017). Currently, one of the best measures for identifying MDD and measuring severity of depressive symptoms is a paper and pencil test – the Patient Health Questionnaire-9 (PHQ-9), which has a sensitivity of 88% and specificity of 88% for major depression (Kroenke et al., 2001).

The range of recommended pharmacotherapy options makes clear that a number of different neurotransmitter systems are implicated in the development of MDD symptomatology. This suggests that all these treatments may have differential effects at varying points on a cascade that creates either a vulnerability for or contributes to the pathogenesis of MDD (Liu et al., 2017). Nevertheless, a diagnostic biomarker for MDD remains elusive. Early theories positing decreased

synaptic concentrations of monoamines underlying the pathogenesis of MDD relied on extrapolating from successful treatment of MDD with medications that increased synaptic availability of monoamines. These monoamine theories of MDD have been discounted as too simplistic, as they fail to address the latency in medication response, and do not account for the many patients that do not respond to treatment with antidepressants (Boku et al., 2018; Racagni & Popoli, 2008).

The Role of Stress in the Pathogenesis of Depression

An expanding body of research in MDD has focused on involvement of the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in the development of the pathogenesis of MDD (Menke, 2019) as well as in development of MDD in perimenopause (Gordon et al., 2015). A further related hypothesis is the neuroplasticity hypothesis of depression (Boku et al., 2018; Racagni & Popoli, 2008), which posits that the derogatory effects of glucocorticoids on neuronal proliferation alters neural morphology and functioning, which can be positively influenced by beneficial effects of brain-derived neurotrophic factor (BDNF) on neural dendrites and spines when antidepressant treatment is initiated in MDD.

The neurobiological response to psychological or physical stress is mediated, at least to some degree, by the HPA axis. A history of early life stress increases the risk for MDD (Bjorkenstam et al., 2017), as does recent life stress (Stegenga et al., 2012), indicating that stress may be an important component in MDD pathogenesis (Liu et al., 2017). Dillon and Pizzagalli (Dillon & Pizzagalli,

2018) have postulated that there is a three-fold effect of physiological stress on processes involved in memory consolidation and retrieval in MDD: suppression of neurogenesis in the hippocampus which leads to impairment in pattern separation and results in impaired memory recollection; inhibition of dopaminergic neurons in the substantia nigra and ventral tegmental area which leads to a reduction in the strength of dopaminergic reward responding, and thus corresponds to impaired encoding and consolidation of positive information; and sensitization of the amygdala, leading to exaggerated amygdala responding, which may result in greater retrieval of negative memories (Dillon & Pizzagalli, 2018).

Studies in MDD report increased cortisol levels (Burke et al., 2005; Cubala & Landowski, 2014; Islam et al., 2018) and hyperactivity of the HPA axis (Pariante & Miller, 2001; Vreeburg et al., 2009) in patients with MDD, compared to healthy control participants. When a threat is perceived, activation of the HPA axis occurs (Raabe & Spengler, 2013). Engagement of the HPA axis results in the release of glucocorticoids that modulate metabolic functions such as liberation of energy stores and pro-inflammatory responding (Sapolsky, 2000a). The hippocampus, an integral part of the glucocorticoid negative feedback circuitry of the HPA axis (Jacobson & Sapolsky, 1991), contains a large concentration of glucocorticoid receptors (De Kloet et al., 1998). Glucocorticoids and stress cause an increase in excitatory amino acids, such as glutamate, in the hippocampal synapse (Sapolsky, 2000b), which can cause glucocorticoid induced atrophy of dendritic processes, which has been correlated with impairment of explicit

memory (Sapolsky, 2000a). In turn, increased hippocampal concentrations of glutamate can reduce neurogenesis in the dentate gyrus by activation of N-methyl-D-aspartate (NMDA) receptors (Cameron et al., 1995), and disrupt glucose transport and metabolism (Sapolsky, 2000b). Prolonged or chronic exposure to increased concentrations of glucocorticoids can disrupt hippocampal functioning (Diamond et al., 2006) and ultimately result in decreases in hippocampal volume (McEwen, 2000; McEwen & Sapolsky, 1995) and medial prefrontal cortex (Willner et al., 2013). Decreased neuroplasticity related to stress mediated by increased remodeling of dendrites, loss of glial cells/increased excitotoxicity, and decreased neurogenesis could result in disruptions in frontotemporal circuitry, decreased hippocampal volume, and greater vulnerability to further MDE (McEwen, 1999; Pittenger & Duman, 2008).

Stress in MDD has been linked with decreases in volume in both medial prefrontal cortex and hippocampus, which are markers of MDD illness progression (Belleau et al., 2019; Treadway et al., 2015). The hippocampus, a structure sensitive to stress, may be involved in the pathogenesis of MDD. While a large multi-site study found no differences in hippocampal volume between healthy comparison participants and patients with first episode MDD (Schmaal et al., 2015), patients with a longer illness duration present with smaller hippocampal volumes (McKinnon et al., 2009) as do patients with multiple episodes of MDD (McKinnon et al., 2009; Schmaal et al., 2015; Videbech & Ravnkilde, 2004), in comparison to healthy participants. The relationship between

illness duration and hippocampal volume may be logarithmic, and indicates that reductions in hippocampal volume may occur at the start of the disease process but not necessarily prior to the development of the first episode of MDD (MacQueen et al., 2003). Nevertheless, some studies have reported no differences in hippocampal volume in MDD (Greenberg et al., 2008; Phillips et al., 2015). In the interim, development of software for automated tissue segmentation has allowed for the analysis of substructures of subcortical regions, including the hippocampus (Fischl et al., 2002). A recent study observed bilateral volume reductions in hippocampal subdivisions including the cornu ammonis (CA) (CA2-CA4), subiculum, and the dentate gyrus, in patients with MDD, compared to comparison participants, with more marked reductions in left hippocampus including more prominent reductions in left CA1 in patients with longer MDD duration, compared to healthy comparison participants, and patients with a first episode of MDD (Roddy et al., 2019). These findings are important for several reasons. Disruption of information transmission through CA substructures of hippocampus may modify processing of sensory and emotional information transmitted through these structures (Roddy et al., 2019). The trisynaptic circuit involves transmission of information through three excitatory glutamatergic synapses from layer II of entorhinal cortex → dentate gyrus → CA3 → CA1 (Stepan et al., 2015). The trisynaptic circuit has been implicated in adult neurogenesis (Schoenfeld et al., 2017). Disruption of the trisynaptic circuit may contribute to impaired processing of sensory and emotional information and thus

contribute to the evolution of symptoms involved in MDD pathogenesis (Roddy et al., 2019). Studies have shown that dentate gyrus and hippocampal CA substructures have been implicated in the effects of stress in depression (Adam Samuels et al., 2015; Samuels & Hen, 2011). Further, a variety of serotonin receptors are represented in CA1 (Berumen et al., 2012), and impaired limbic serotonergic neurotransmission could occur as a result of disruptions in CA1 functioning, or having a large representation of serotonergic receptor subtypes makes CA1 vulnerable to imbalances in the serotonergic system (Roddy et al., 2019). Extended exposure of animals to corticosteroids diminishes serotonergic responding in CA1 (Karten et al., 1999). Extended exposure to cortisol in humans could result in disruptions to the serotonergic system and corresponding reduction in volume in CA1 in the hippocampus (Roddy et al., 2019), and compared to healthy comparisons participants, patients with MDD demonstrate lower levels of hippocampal serotonin receptor 1_A messenger ribonucleic acid levels (López-Figueroa et al., 2004). However, meta-analyses report no significant differences in serotonin reuptake sites in medial prefrontal cortex (Gryglewski et al., 2014) or in serotonin transporters in hippocampus (Gryglewski et al., 2014)in patients with MDD compared to healthy control participants.

Neuroplasticity in Depression

Neuroplasticity may be defined as the capacity of the brain to make modifications to adapt to novel circumstances (Demarin et al., 2014). Neuroplasticity may occur in response to stress, and abnormal neuroplastic alterations in the brain may be a

causal factor in psychiatric disorders, such as MDD (Liu et al., 2017). There are three pillars supporting the neuroplasticity hypothesis of depression (Liu et al., 2017). The first is the neuroplastic changes documented in hippocampus and prefrontal cortex in patients with MDD, that result in reduced volume (Koolschijn et al., 2009; Roddy et al., 2019), histological changes (Cobb et al., 2013; Cotter et al., 2002), and functional impairments (Campbell & MacQueen, 2004; Snyder, 2013) in these structures. Further supporting evidence includes reduced peripheral concentrations of BDNF in individuals with MDD compared to healthy comparison participants (Kishi et al., 2018). BDNF is important for maintaining neuronal health, differentiation and regulating synaptic plasticity (Anderson, 1998). Finally, electroconvulsive therapy, conventional antidepressant drugs, and N-methyl-D-aspartate (NMDA) receptor agonist ketamine, have been shown to effect change by elevating serum concentrations of BDNF (Bjorkholm & Monteggia, 2016). Successful response to antidepressants is also associated with increased volume in hippocampus (Dusi et al., 2015; Frodl et al., 2008) and in prefrontal cortex (Dusi et al., 2015), and alters functional neuroplasticity in hippocampus and prefrontal cortex (Wessa & Lois, 2015).

This dissertation aims to further characterize what is known about neuroplasticity in MDD in a selection of patient groups experiencing depression. Changes in hippocampal volume have been observed in MDD (McKinnon et al., 2009; Roddy et al., 2019; Schmaal et al., 2015; Videbech & Ravnkilde, 2004). While there is some debate as to whether these changes precede MDD or occur as

a result of MDD (Schmaal et al., 2015), these changes may be associated with alterations in hippocampal-dependent memory in patients with recurrent depression, including during the euthymic phase (Campbell & MacQueen, 2004). Antidepressant treatment has been shown to increase hippocampal volume in patients with MDD (Dusi et al., 2015; Frodl et al., 2008). Observations of an increase in hippocampal volume in the first stages of antidepressant treatment in MDD patients that are medication naïve, may be associated with clinical response, and further bolsters the theory that hippocampal neuroplasticity is important in mediating the antidepressant treatment response in MDD (Fu et al., 2015). There is some evidence that hippocampal function in patients with MDD may be altered before changes in volume are observed (MacQueen et al., 2003), and a number of studies have reported impairment in hippocampal-dependent memory in patients with MDD (MacQueen et al., 2002; Zakzanis et al., 1998). Chapter 2 discusses patterns of alterations in hippocampal functioning with preserved cognitive performance in patients with MDD that have received antidepressant treatment for MDD, completing a hippocampus-dependent process-dissociation memory task. Thus, this chapter will address hippocampal functioning in patients with MDD early in the disease process, and prior to starting antidepressant treatment.

Heightened risk of developing MDD has been observed in some midlife women in the menopausal transition (Bromberger et al., 2015), and the menopausal transition is characterized by increased symptoms of depression (Santoro, 2016). Hormone therapy (HT) is the standard treatment for menopausal

symptoms including vasomotor, and genitourinary symptoms (The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). In addition to quelling these symptoms, perimenopausal women receiving treatment with transdermal 17 β Estradiol also report fewer depressive symptoms (Gordon & Girdler, 2014; Schmidt et al., 2000; Soares et al., 2001), and a recent study has demonstrated promising results that HT may ameliorate the risk for developing depressive symptoms in perimenopausal women (Gordon et al., 2018). Estrogen therapy may decrease mood symptoms by exerting modulatory effects on serotonin, a neurotransmitter important for cognition and mood (Lokuge et al., 2011). We sought to characterize the modulatory effect of estrogen therapy on mood and functional neural activity through the interaction of estrogen with the serotonergic system, by employing an acute tryptophan depletion paradigm. This paradigm reduces availability of the amino acid tryptophan, the rate-limiting precursor for serotonin production (Fernstrom et al., 2013; Richard et al., 2009; Schaechter & Wurtman, 1990), and therefore reduces neural serotonin levels. Chapter 3 introduces results from this fMRI acute tryptophan depletion study using an emotional conflict task that examine changes in mood and functional neural activity in emotional information processing in a group of perimenopausal women receiving treatment with estrogen.

Chapter 4 characterizes and compares behavioural and functional neural activity in patients with MDD prior to treatment begin, via a series of cognitive tasks and an fMRI emotional information processing task.

In Chapter 5, this same group of participants is further divided into patients with MDD who reach remission after 8 weeks of treatment with escitalopram, patients who reach remission after 16 weeks of treatment with a combination of escitalopram and adjunctive aripiprazole, and patients who do not reach remission after 16 weeks of treatment with escitalopram plus adjunctive aripiprazole. The behavioural and neural activity of these three groups of participants with MDD on an emotional conflict task is characterized and compared at baseline and after 8 weeks of treatment.

Chapter 6 presents results of a volumetric MRI analysis of a patient with severe ventriculomegaly presenting with primarily depressive mood symptoms.

Chapter 7 provides a discussion of the strengths and weaknesses of each of these studies, explains the significance of this body of research, and offers future directions.

References

Adam Samuels, B., Leonardo, E. D., & Hen, R. (2015). Hippocampal subfields and Major Depressive Disorder. *Biol Psychiatry,* 77(3), 210-211. doi:10.1016/j.biopsych.2014.11.007

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (Fifth Edition ed.).

American Psychiatric Association. (2014). Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. Retrieved from https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm04

Aronson, J. K., & Ferner, R. E. (2017). Biomarkers - a general review. *Curr Protoc Pharmacol,* 76, 9.23.21-29.23.17. doi:10.1002/cpph.19

Belleau, E. L., Treadway, M. T., & Pizzagalli, D. A. (2019). The impact of stress and Major Depressive Disorder on hippocampal and medial prefrontal cortex morphology. *Biol Psychiatry,* 85(6), 443-453. doi:10.1016/j.biopsych.2018.09.031

Bennabi, D., Vandel, P., Papaxanthis, C., Pozzo, T., & Haffen, E. (2013). Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. *Biomed Res Int,* 2013, 158746. doi:10.1155/2013/158746

Berger, A. (2002). Magnetic resonance imaging. *BMJ,* 324(7382), 35. doi:10.1136/bmj.324.7328.35

Berumen, L. C., Rodríguez, A., Miledi, R., & García-Alcocer, G. (2012). Serotonin receptors in hippocampus. *TheScientificWorldJournal,* 2012, 823493-823493. doi:10.1100/2012/823493

Bjorkenstam, E., Vinnerljung, B., & Hjern, A. (2017). Impact of childhood adversities on depression in early adulthood: A longitudinal cohort study of 478,141 individuals in Sweden. *J Affect Disord,* 223, 95-100. doi:10.1016/j.jad.2017.07.030

Bjorkholm, C., & Monteggia, L. M. (2016). BDNF - a key transducer of antidepressant effects. *Neuropharmacology,* 102, 72-79. doi:10.1016/j.neuropharm.2015.10.034

Bloch, M., Schmidt, P. J., Danaceau, M., Murphy, J., Nieman, L., & Rubinow, D. R. (2000). Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry,* 157, 924-930. doi:10.1176/appi.ajp.157.6.924

Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of Major Depressive Disorder: beyond monoamine hypothesis. *Psychiatry Clin Neurosci,* 72(1), 3-12. doi:10.1111/pcn.12604

Bouhuys, A. L., Geerts, E., & Gordijn, M. C. (1999). Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. *J Nerv Ment Dis,* 187(10), 595-602. doi:10.1097/00005053-199910000-00002

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in Major Depression: a review. *Aust N Z J Psychiatry,* 44, 681-696. doi:10.3109/00048674.2010.496359

Bromberger, J. T., & Epperson, C. N. (2018). Depression during and after the perimenopause: Impact of hormones, genetics, and environmental determinants of disease. *Obstet Gynecol Clin North Am,* 45(4), 663-678. doi:10.1016/j.ogc.2018.07.007

Bromberger, J. T., Kravitz, H. M., Chang, Y. F., Cyranowski, J. M., Brown, C., & Matthews, K. A. (2011). Major Depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med,* 41(09), 1879-1888. doi:10.1017/s003329171100016x

Bromberger, J. T., Schott, L., Kravitz, H. M., & Joffe, H. (2015). Risk factors for major depression during midlife among a community sample of women with and without prior Major Depression: are they the same or different? *Psychol Med,* 45(8), 1653-1664. doi:10.1017/S0033291714002773

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

Cameron, H. A., McEwen, B. S., & Gould, E. (1995). Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *J Neurosci,* 15(6), 4687-4692. doi:10.1523/JNEUROSCI.15-06-04687.1995

Campbell, S., & MacQueen, G. M. (2004). The role of the hippocampus in the pathophysiology of Major Depression. *J Psychiatry Neurosci,* 29(6), 417-426. Retrieved from /pmc/articles/PMC524959/?report=abstract

Chiu, M., Lebenbaum, M., Cheng, J., de Oliveira, C., & Kurdyak, P. (2017). The direct healthcare costs associated with psychological distress and Major Depression: a population-based cohort study in Ontario, Canada. *PLoS One,* 12(9), e0184268. doi:10.1371/journal.pone.0184268

Chow, W., Doane, M. J., Sheehan, J., Alphs, L., & Le, H. (2019). Economic burden among patients with Major Depressive Disorder: an analysis of healthcare resource use, work productivity, and direct and indirect costs by depression severity. *AJMC*, 1-4. doi:10.15252/embr.201642951

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., . . . Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with Major Depressive Disorder: a systematic review and network meta-analysis. *Lancet,* 391(10128), 1357-1366. doi:10.1016/s0140-6736(17)32802-7

Cobb, J. A., Simpson, J., Mahajan, G. J., Overholser, J. C., Jurjus, G. J., Dieter, L., . . . Stockmeier, C. A. (2013). Hippocampal volume and total cell numbers in Major Depressive Disorder. *J Psychiatr Res,* 47(3), 299-306. doi:10.1016/j.jpsychires.2012.10.020

Cohen, L. S., Soares, C. N., Vitonis, A. F., Otto, M. W., & Harlow, B. L. (2006). Risk for new onset depression during the menopausal transition. *Arch Gen Psychiatry,* 63, 385-390. doi:10.1001/archpsyc.63.4.385

Cotter, D., Mackay, D., Chana, G., Beasley, C., Landau, S., & Everall, I. P. (2002). Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with Major Depressive Disorder. *Cereb Cortex,* 12(4), 386-394. doi:10.1093/cercor/12.4.386

Cyranowski, J. M., Frank, E., Young, E., & Shear, K. (2000). Adolescent onset of the gender difference in lifetime rates of Major Depression: A theoretical model. *Arch Gen Psychiatry,* 57(1), 21-27. doi:10.1001/archpsyc.57.1.21

Dalili, M. N., Penton-Voak, I. S., Harmer, C. J., & Munafò, M. R. (2015). Meta-analysis of emotion recognition deficits in Major Depressive Disorder. *Psychol Med*, 1135-1144. doi:10.1017/S0033291714002591

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocr Reviews,* 19(3), 269-301. doi:10.1210/edrv.19.3.0331

Demarin, V., Morović, S., & Béné, R. (2014). Neuroplasticity. *Periodicum Biologorum,* 116(2), 209-211. Retrieved from <Go to ISI>://WOS:000341406500015

Diamond, D. M., Campbell, A. M., Park, C. R., Woodson, J. C., Conrad, C. D., Bachstetter, A. D., & Mervis, R. F. (2006). Influence of predator stress on the consolidation versus retrieval of long-term spatial memory and hippocampal spinogenesis. *Hippocampus,* 16(7), 571-576. doi:10.1002/hipo.20188

Dillon, D. G., & Pizzagalli, D. A. (2018). Mechanisms of memory disruption in depression. *Trends Neurosci,* 41(3), 137-149. doi:10.1016/j.tins.2017.12.006

Dusi, N., Barlati, S., Vita, A., & Brambilla, P. (2015). Brain structural effects of antidepressant treatment in Major Depression. *Current neuropharmacology,* 13(4), 458-465. doi:10.2174/1570159X1304150831121909

Eaton, W. W., Anthony, J. C., Gallo, J., Cai, G., Tien, A., Romanoski, A., . . . Chen, L. (1997). Natural history of diagnostic interview schedule/DSM-IV Major Depression. *Arch Gen Psychiatry,* 54(11), 993-999. doi:10.1001/archpsyc.1997.01830230023003

Eaton, W. W., Shao, H., Nestadt, G., Lee, B. H., Bienvenu, O. J., & Zandi, P. (2008). Population-based study of first onset and chronicity in Major Depressive Disorder. *Arch Gen Psychiatry,* 65(5), 513-520. doi:10.1001/archpsyc.65.5.513

Egede, L. E., & Hernández-Tejada, M. A. (2013). Effect of comorbid depression on quality of life in adults with Type 2 diabetes. *Expert Rev Pharmacoecon Outcomes Res,* 13(1), 83-91. doi:10.1586/erp.12.86

Elster, A. D. (2018a). BOLD Signal. *Questions and Answers in MRI*. Retrieved from http://mriquestions.com/why-does-bold-uarr-signal.html

Elster, A. D. (2018b). Precession vs Resonance. *Questions and Answers in MRI*. Retrieved from http://mriquestions.com/does-precession--nmr.html

Fernstrom, J. D., Langham, K. A., Marcelino, L. M., Irvine, Z. L., Fernstrom, M. H., & Kaye, W. H. (2013). The ingestion of different dietary proteins by humans induces large changes in the plasma tryptophan ratio, a predictor of brain tryptophan uptake and serotonin synthesis. *Clin Nutr,* 32(6), 1073-1076. doi:10.1016/j.clnu.2012.11.027

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., . . . Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Med.,* 10(11), e1001547. doi:10.1371/journal.pmed.1001547

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., . . . Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron,* 33(3), 341-355. doi:10.1016/S0896-6273(02)00569-X

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci USA,* 83(4), 1140-1144. doi:10.1073/pnas.83.4.1140

Freeman, E. W., Sammel, M. D., Lin, H., & Nelson, D. B. (2006). Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry,* 63(4), 375-382. doi:10.1001/archpsyc.63.4.375

Freeman, E. W., Sammel, M. D., Liu, L., Gracia, C. R., Nelson, D. B., & Hollander, L. (2004). Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry,* 61, 62-70. doi:10.1001/archpsyc.61.1.62

Frey, B. N., & Soares, C. N. (2009). Managing depression and anxiety during the menopausal transition and beyond: the window of vulnerability. In C. N. Soares & M. Warren (Eds.), *The Menopausal Transition. Interface between Gynecology and Psychiatry. Key Issues in Mental Health* (Vol. 175, pp. 102-114). Basel: Karger.

Frodl, T., Jäger, M., Smajstrlova, I., Born, C., Bottlender, R., Palladino, T., . . . Meisenzahl, E. M. (2008). Effect of hippocampal and amygdala volumes on clinical outcomes in Major Depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci,* 33(5), 423-430. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18787661 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527720/

Fu, C. H. Y., Costafreda, S. G., Sankar, A., Adams, T. M., Rasenick, M. M., Liu, P., . . . Marangell, L. B. (2015). Multimodal functional and structural neuroimaging investigation of Major Depressive Disorder following treatment with duloxetine. *BMC Psychiatry,* 15(1), 82. doi:10.1186/s12888-015-0457-2

Furukawa, T. A., Cipriani, A., Atkinson, L. Z., Leucht, S., Ogawa, Y., Takeshima, N., . . . Salanti, G. (2016). Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. *Lancet Psychiatry,* 3(11), 1059-1066. doi:10.1016/s2215-0366(16)30307-8

Furukawa, T. A., Cipriani, A., Leucht, S., Atkinson, L. Z., Ogawa, Y., Takeshima, N., . . . Salanti, G. (2018). Is placebo response in antidepressant trials rising or not? A reanalysis of datasets to conclude this long-lasting controversy. *Evid Based Mental Health,* 21(1), 1-3. doi:10.1136/eb-2017-102827

Gao, S., Calhoun, V. D., & Sui, J. (2018). Machine learning in major depression: From classification to treatment outcome prediction. *CNS Neurosci Ther,* 24(11), 1037-1052. doi:10.1111/cns.13048

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., & Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet,* 361(9358), 653-661. doi:10.1016/s0140-6736(03)12599-8

Girgus, J. S., Yang, K., & Ferri, C. V. (2017). The gender difference in depression: Are elderly women at greater risk for depression than elderly men? *Geriatrics,* 2(4: 35), 1-21. doi:10.3390/geriatrics2040035

Gordon, J. L., & Girdler, S. S. (2014). Hormone replacement therapy in the treatment of perimenopausal depression. *Curr Psychiatry Rep,* 16(12), 517. doi:10.1007/s11920-014-0517-1

Gordon, J. L., Girdler, S. S., Meltzer-Brody, S. E., Stika, C. S., Thurston, R. C., Clark, C. T., . . . Wisner, K. L. (2015). Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. *Am J Psychiatry,* 172(3), 227-236. doi:10.1176/appi.ajp.2014.14070918

Gordon, J. L., Rubinow, D. R., Eisenlohr-Moul, T. A., Xia, K., Schmidt, P. J., & Girdler, S. S. (2018). Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause

transition: a randomized clinical trial. *JAMA Psychiatry,* 75(2), 149-157. doi:10.1001/jamapsychiatry.2017.3998

Gotlib, I. H., Jonides, J., Buschkuehl, M., & Joormann, J. (2011). Memory for affectively valenced and neutral stimuli in depression: evidence from a novel matching task. *Cogn Emot,* 25(7), 1246-1254. doi:10.1080/02699931.2010.538374

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol,* 6, 285-312. doi:10.1146/annurev.clinpsy.121208.131305

Greenberg, D. L., Payne, M. E., MacFall, J. R., Steffens, D. C., & Krishnan, R. R. (2008). Hippocampal volumes and depression subtypes. *Psychiatry Res,* 163(2), 126-132. doi:10.1016/j.pscychresns.2007.12.009

Hammar, A., & Ardal, G. (2009). Cognitive functioning in Major Depression--a summary. *Front Hum Neurosci,* 3, 26. doi:10.3389/neuro.09.026.2009

Hantsoo, L., & Epperson, C. N. (2015). Premenstrual Dysphoric Disorder: epidemiology and treatment. *Curr Psychiatry Rep,* 17(11), 87. doi:10.1007/s11920-015-0628-3

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci,* 368(1615), 20120407. doi:10.1098/rstb.2012.0407

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry,* 4(5), 409-418. doi:10.1016/s2215-0366(17)30015-9

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord,* 134(1-3), 20-31. doi:10.1016/j.jad.2010.11.011

Hickie, I., Naismith, S., Ward, P. B., Turner, K., Scott, E., Mitchell, P., . . . Parker, G. (2005). Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br J Psychiatry,* 186, 197-202. doi:10.1192/bjp.186.3.197

Inoue, Y., Yamada, K., & Kanba, S. (2006). Deficit in theory of mind is a risk for relapse of Major Depression. *J Affect Disord,* 95(1-3), 125-127. doi:10.1016/j.jad.2006.04.018

Ishak, W. W., Balayan, K., Bresee, C., Greenberg, J. M., Fakhry, H., Christensen, S., & Rapaport, M. H. (2013). A descriptive analysis of quality of life using patient-reported measures in Major Depressive Disorder in a naturalistic outpatient setting. *Qual Life Res,* 22(3), 585-596. doi:10.1007/s11136-012-0187-6

Ishak, W. W., Mirocha, J., Christensen, S., Wu, F., Kwock, R., Behjat, J., . . . Elashoff, D. (2014). Patient-reported outcomes of quality of life, functioning, and depressive symptom severity in Major Depressive Disorder comorbid with Panic Disorder before and after SSRI treatment in the STAR*D trial. *Depress Anxiety,* 31(8), 707-716. doi:10.1002/da.22152

Islam, M., Islam, M., Ahmed, I., Moktadir, A., Nahar, Z., Islam, M., . . . Hasnat, A. (2018). Elevated serum levels of malondialdehyde and cortisol are associated with major depressive disorder: A case-control study. *SAGE Open Medicine,* 6, 1-7. doi:10.1177/2050312118773953

Ivanova, J. I., Birnbaum, H. G., Kidolezi, Y., Subramanian, G., Khan, S. A., & Stensland, M. D. (2010). Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant Major Depressive Disorder. *Curr Med Res Opin,* 26(10), 2475-2484. doi:10.1185/03007995.2010.517716

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Reviews,* 12(2), 118-134. doi:10.1210/edrv-12-2-118

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in Major Depressive Disorder. *Psychiatry Res,* 145(1), 39-48. doi:10.1016/j.psychres.2005.11.011

Jorge, J., Figueiredo, P., Gruetter, R., & van der Zwaag, W. (2018). Mapping and characterization of positive and negative BOLD responses to visual stimulation in multiple brain regions at 7T. *Hum Brain Mapp,* 39(6), 2426-2441. doi:10.1002/hbm.24012

Karten, Y. J., Nair, S. M., van Essen, L., Sibug, R., & Joëls, M. (1999). Long-term exposure to high corticosterone levels attenuates serotonin responses in rat hippocampal CA1 neurons. *Proc Natl Acad Sci USA,* 96(23), 13456-13461. doi:10.1073/pnas.96.23.13456

Kaymaz, N., van Os, J., Loonen, A. J. M., & Nolen, W. A. (2008). Evidence that patients with single versus recurrent depressive epsiodes are differentially

sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry,* 69(9), 1423-1436.

Kennedy, S. (2002). Full remission: a return to normal functioning. *J Psychiatry Neurosci,* 27(4), 233-234. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12174731

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., . . . Group, C. D. W. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry,* 61(9), 540-560. doi:10.1177/0706743716659417

Kessler, R. C. (2012). The costs of depression. *Psychiatr Clin North Am,* 35(1), 1-14. doi:10.1016/j.psc.2011.11.005

Kessler, R. C., & Walters, E. E. (1998). Epidemiology of DSM-III-R Major Depression and Minor Depression among adolescent and young adults in the National Comorbidity Survey. *Depress Anxiety,* 7, 3-14. doi:10.1002/(SICI)1520-6394(1998)7:1<3::AID-DA2>3.0.CO;2-F

Kessler, R. C., Zhao, S., Blazer, D. G., & Swartz, M. (1997). Prevalence, correlates, and course of Minor Depression and Major Depression in the national comorbidity survey. *J Affect Disord,* 45(1-2), 19-30. doi:10.1016/S0165-0327(97)00056-6

Kishi, T., Yoshimura, R., Ikuta, T., & Iwata, N. (2018). Brain-derived neurotrophic factor and Major Depressive Disorder: evidence from meta-analyses. *Front Psychiatry,* 8, 308-308. doi:10.3389/fpsyt.2017.00308

Knoll, A. D., & MacLennan, R. N. (2017). Prevalence and correlates of depression in Canada: findings from the Canadian Community Health Survey. *Can Psychol,* 58(2), 116-123. doi:10.1037/cap0000103

Koolschijn, P. C. M. P., van Haren, N. E. M., Lensvelt-Mulders, G. J. L. M., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in Major Depressive Disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp,* 30(11), 3719-3735. doi:10.1002/hbm.20801

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9 validity of a brief depression severity measure. *J Gen Intern Med,* 16(9), 606-613. doi:10.1046/j.1525-1497.2001.016009606.x

Kuehner, C. (2017). Why is depression more common among women than among men? *Lancet Psychiatry,* 4(2), 146-158. doi:10.1016/s2215-0366(16)30263-2

Ladegaard, N., Videbech, P., Lysaker, P. H., & Larsen, E. R. (2016). The course of social cognitive and metacognitive ability in depression: deficit are only partially normalized after full remission of first episode Major Depression. *Br J Clin Psychol,* 55(3), 269-286. doi:10.1111/bjc.12097

Lam, R. W., Kennedy, S. H., McLntyre, R. S., & Khullar, A. (2014). Cognitive dysfunction in Major Depressive Disorder: effects on psychosocial functioning and implications for treatment. *Can J Psychiatry,* 59(12), 649-654. doi:10.1177/070674371405901206

Lam, R. W., McIntosh, D., Wang, J., Enns, M. W., Kolivakis, T., Michalak, E. E., . . . Group, C. D. W. (2016a). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. *Can J Psychiatry,* 61(9), 510-523. doi:10.1177/0706743716659416

Lam, R. W., Milev, R., Rotzinger, S., Andreazza, A. C., Blier, P., Brenner, C., . . . and on behalf of the CAN-BIND Investigator Team. (2016b). Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. *BMC Psychiatry,* 16(1), 105. doi:10.1186/s12888-016-0785-x

Lin, E., Kuo, P. H., Liu, Y. L., Yu, Y. W., Yang, A. C., & Tsai, S. J. (2018). A deep learning approach for predicting antidepressant response in Major Depression using clinical and genetic biomarkers. *Front Psychiatry,* 9, 290. doi:10.3389/fpsyt.2018.00290

Liu, B., Liu, J., Wang, M., Zhang, Y., & Li, L. (2017). From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. *Front Cell Neurosci,* 11, 305. doi:10.3389/fncel.2017.00305

Logothetis, N. K. (2003). The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci,* 23(10), 3963-3971. doi:10.1523/JNEUROSCI.23-10-03963.2003

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature,* 453(7197), 869-878. doi:10.1038/nature06976

Lokuge, S., Frey, B. N., Foster, J. A., Soares, C. N., & Steiner, M. (2011). Depression in women: windows of vulnerability and new insights into the link between estrogen and serotonin. *J Clin Psychiatry,* 72(11), e1563-1569. doi:10.4088/JCP.11com07089

MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., . . . Young, L. T. (2003). Course of illness, hippocampal function, and hippocampal volume in Major Depression. *Proc Natl Acad Sci USA,* 100(3), 1387-1392. doi:10.1073/pnas.0337481100

MacQueen, G. M., Frey, B. N., Ismail, Z., Jaworska, N., Steiner, M., Lieshout, R. J., . . . Group, C. D. W. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly. *Can J Psychiatry,* 61(9), 588-603. doi:10.1177/0706743716659276

MacQueen, G. M., Galway, T. M., Hay, J., Young, L. T., & Joffe, R. T. (2002). Recollection memory deficits in patients with Major Depressive Disorder predicted by past depressions but not current mood state or treatment status. *Psychol Med,* 32(2), 251-258. doi:10.1017/S0033291701004834

Maeshima, H., Baba, H., Satomura, E., Shimano, T., Inoue, M., Ishijima, S., . . . Arai, H. (2016). Residual memory impairment in remitted depression may be a predictive factor for recurrence. *J Clin Psychiatry,* 77(2), 247-251. doi:10.4088/JCP.14m09694

Maki, P. M., Kornstein, S. G., Joffe, H., Bromberger, J. T., Freeman, E. W., Athappilly, G., . . . Mood Disorders Task Force of the National Network of Depression, C. (2018). Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause,* 25(10), 1069-1085. doi:10.1097/GME.0000000000001174

Marcus, S. M. (2009). Depression during pregnancy: rates, risks and consequences--Motherisk Update 2008. *Can J Clin Pharmacol,* 16(1), e15-22. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19164843

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annu Rev Neurosci,* 22(1), 105-122. doi:10.1146/annurev.neuro.22.1.105

McEwen, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biol Psychiatry,* 48(8), 721-731. doi:10.1016/S0006-3223(00)00964-1

McEwen, B. S., & Sapolsky, R. M. (1995). Stress and cognitive function. *Curr Opin Neurobiology,* 5(2), 205-216. doi:10.1016/0959-4388(95)80028-X

McIntyre, R. S., & Lee, Y. (2016). Cognition in major depressive disorder: a 'Systemically Important Functional Index' (SIFI). *Curr Opin Psychiatry,* 29(1), 48-55. doi:10.1097/YCO.0000000000000221

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with Major Depressive Disorder. *J Psychiatry Neurosci,* 34(1), 41-54. Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19125212&retmode=ref&cmd=prlinks

Menke, A. (2019). Is the HPA axis as target for depression outdated, or is there a new hope? *Front Psychiatry,* 10, 101. doi:10.3389/fpsyt.2019.00101

Milev, R. V., Giacobbe, P., Kennedy, S. H., Blumberger, D. M., Daskalakis, Z. J., Downar, J., . . . Group, C. D. W. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. *Can J Psychiatry,* 61(9), 561-575. doi:10.1177/0706743716660033

Mitchell, H. H., Hamilton, T. S., Steggerda, F. R., & Bean, H. W. (1945). The chemical composition of the adult human and its bearing on the biochemistry of growth. *J Biol Chem,* 158, 625-637.

Mykletun, A., Bjerkeset, O., Overland, S., Prince, M., Dewey, M., & Stewart, R. (2009). Levels of anxiety and depression as predictors of mortality: the HUNT study. *Br J Psychiatry,* 195(2), 118-125. doi:10.1192/bjp.bp.108.054866

Novick, D., Montgomery, W., Vorstenbosch, E., Moneta, M. V., Duenas, H., & Haro, J. M. (2017). Recovery in patients with major depressive disorder (MDD): results of a 6-month, multinational, observational study. *Patient Prefer Adherence,* 11, 1859-1868. doi:10.2147/PPA.S138750

Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in Major Depression: relevance to pathophysiology and treatment. *Biol Psychiatry,* 49(5), 391-404. doi:10.1016/S0006-3223(00)01088-X

Paykel, E. S. (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues Clin Neurosci,* 10(4), 431-437. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19170400

Paykel, E. S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychol Med,* 25(6), 1171-1180. doi:10.1017/S0033291700033146

Pearson, C., Janz, T., & Ali, J. (2013). *Mental and substance use disorders in Canada*. Retrieved from http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11855-eng.htm

https://www150.statcan.gc.ca/n1/en/pub/82-624-x/2013001/article/11855-eng.pdf?st=qTucwPia

Phillips, J. L., Batten, L. A., Tremblay, P., Aldosary, F., & Blier, P. (2015). A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. *Int J Neuropsychopharmacol,* 18(8), pyv037-pyv037. doi:10.1093/ijnp/pyv037

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology,* 33(1), 88-109. doi:10.1038/sj.npp.1301574

Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2012). *Handbook of Functional MRI Data Analysis*. New York, USA: Cambridge University Press.

Raab, P. A., Mackintosh, M. A., Gros, D. F., & Morland, L. A. (2015). Impact of comorbid depression on quality of life in male combat veterans with posttraumatic stress disorder. *J Rehabil Res Dev,* 52(5), 563-576. doi:10.1682/jrrd.2014.05.0130

Raabe, F. J., & Spengler, D. (2013). Epigenetic risk factors in PTSD and depression. *Front Psychiatry,* 4, 80. doi:10.3389/fpsyt.2013.00080

Racagni, G., & Popoli, M. (2008). Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues Clin Neurosci,* 10(4), 385-400. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19170396

Rai, D., Zitko, P., Jones, K., Lynch, J., & Araya, R. (2013). Country- and individual-level socioeconomic determinants of depression: multilevel

cross-national comparison. *Br J Psychiatry,* 202(3), 195-203. doi:10.1192/bjp.bp.112.112482

Richard, D. M., Dawes, M. A., Mathias, C. W., Acheson, A., Hill-Kapturczak, N., & Dougherty, D. M. (2009). L-Tryptophan: basic metabolic functions, behavioral research and therapeutic indications. *Int J Tryptophan Res,* 2, 45-60. doi:10.4137/IJTR.S2129

Rizvi, S. J., Grima, E., Tan, M., Rotzinger, S., Lin, P., McIntyre, R. S., & Kennedy, S. H. (2014). Treatment-resistant depression in primary care across Canada. *Can J Psychiatry,* 59(7), 349-357. doi:10.1177/070674371405900702

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med,* 44(10), 2029-2040. doi:10.1017/S0033291713002535

Roddy, D. W., Farrell, C., Doolin, K., Roman, E., Tozzi, L., Frodl, T., . . . O'Hanlon, E. (2019). The hippocampus in depression: more than the sum of its parts? Advanced hippocampal substructure segmentation in depression. *Biol Psychiatry,* 85(6), 487-497. doi:10.1016/j.biopsych.2018.08.021

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS Spectrums,* 18(3), 139-149. doi:10.1017/S1092852913000072

Rubinow, D. R., Hoban, M. C., Grover, G. N., Galloway, D. S., Roy-Byrne, P., Andersen, R., & Merriam, G. R. (1988). Changes in plasma hormones across the menstrual cycle in patients with menstrually related mood disorder and in control subjects. *Am J Obstet Gynecol,* 158(1), 5-11. doi:10.1016/0002-9378(88)90765-x

Ruiz, N. A. L., Del Angel, D. S., Olguin, H. J., & Silva, M. L. (2018). Neuroprogression: the hidden mechanism of depression. *Neuropsychiatr Dis Treat,* 14, 2837-2845. doi:10.2147/NDT.S177973

Samuels, B. A., & Hen, R. (2011). Neurogenesis and affective disorders. *Eur J Neurosci,* 33(6), 1152-1159. doi:10.1111/j.1460-9568.2011.07614.x

Santoro, N. (2016). Perimenopause: from research to practice. *J Womens Health (Larchmt),* 25(4), 332-339. doi:10.1089/jwh.2015.5556

Sapolsky, R. M. (2000a). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry,* 57(10), 925-935. doi:10.1001/archpsyc.57.10.925

Sapolsky, R. M. (2000b). The possibility of neurotoxicity in the hippocampus in Major Depression: a primer on neuron death. *Biol Psychiatry,* 48(8), 755-765. doi:10.1016/S0006-3223(00)00971-9

Saragoussi, D., Christensen, M. C., Hammer-Helmich, L., Rive, B., Touya, M., & Haro, J. M. (2018). Long-term follow-up on health-related quality of life in Major Depressive Disorder: a 2-year European cohort study. *Neuropsychiatr Dis Treat,* 14, 1339-1350. doi:10.2147/NDT.S159276

Schaechter, J. D., & Wurtman, R. J. (1990). Serotonin release varies with brain tryptophan levels. *Brain Res,* 5(1-2), 203-210. doi:10.1016/0006-8993(90)91761-5

Scheele, D., Mihov, Y., Schwederski, O., Maier, W., & Hurlemann, R. (2013). A negative emotional and economic judgment bias in Major Depression. *Eur Arch Psychiatry Clin Neurosci,* 263(8), 675-683. doi:10.1007/s00406-013-0392-5

Schmaal, L., Veltman, D. J., van Erp, T. G., Samann, P. G., Frodl, T., Jahanshad, N., . . . Hibar, D. P. (2015). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry,* 21(6), 806-812. doi:10.1038/mp.2015.69

Schmidt, P. J., Nieman, L., Danaceau, M. A., Tobin, M. B., Roca, C. A., Murphy, J. H., & Rubinow, D. R. (2000). Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol,* 183(2), 414-420. doi:10.1067/mob.2000.106004

Schoenfeld, T. J., McCausland, H. C., Morris, H. D., Padmanaban, V., & Cameron, H. A. (2017). Stress and loss of adult neurogenesis differentially reduce hippocampal volume. *Biol Psychiatry,* 82(12), 914-923. doi:10.1016/j.biopsych.2017.05.013

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry,* 3(5), 425-435. doi:10.1016/s2215-0366(16)00012-2

Simmons, L. A., Braun, B., Charnigo, R., Havens, J. R., & Wright, D. W. (2008). Depression and poverty among rural women: A relationship of social causation or social selection? *J Rural Health,* 24(3), 292 - 298. doi:DOI 10.1111/j.1748-0361.2008.00171.x

Snyder, H. R. (2013). Major Depressive Disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological bulletin,* 139(1), 81-132. doi:10.1037/a0028727

Soares, C. N., Almeida, O. P., Joffe, H., & Cohen, L. S. (2001). Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry,* 58, 529-534. doi:10.1001/archpsyc.58.6.529

Soares, C. N., & Zitek, B. (2008). Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci,* 33(4), 331-343. Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18592034&retmode=ref&cmd=prlinks

Sobocki, P., Jonsson, B., Angst, J., & Rehnberg, C. (2006). Cost of depression in Europe. *J Ment Health Policy Econ,* 9(2), 87-98. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17007486

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Lavori, P. W., Shea, T., . . . Endicott, J. (2000). Multiple recurrences of Major Depressive Disorder. *Am J Psychiatry,* 157, 229-233. doi:10.1176/appi.ajp.157.2.229

Spijker, J., de Graaf, R., Bijl, R. V., Beekman, A. T. F., Ormel, J., & Nolen, W. A. (2002). Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Br J Psychiatry,* 181, 208-213. doi:10.1192/bjp.181.3.208

Stegenga, B. T., Nazareth, I., Grobbee, D. E., Torres-Gonzalez, F., Svab, I., Maaroos, H. I., . . . Geerlings, M. I. (2012). Recent life events pose greatest risk for onset of Major Depressive Disorder during mid-life. *J Affect Disord,* 136(3), 505-513. doi:10.1016/j.jad.2011.10.041

Steiner, M. (2003). Hormones and mood: from menarche to menopause and beyond. *J Affect Disord,* 74(1), 67-83. doi:10.1016/s0165-0327(02)00432-9

Stepan, J., Dine, J., & Eder, M. (2015). Functional optical probing of the hippocampal trisynaptic circuit in vitro: network dynamics, filter properties, and polysynaptic induction of CA1 LTP. *Front Neurosci,* 9, 160. doi:10.3389/fnins.2015.00160

Stewart, W. F., Ricci, J. A., Chee, E., Hahn, S. R., & Morganstein, D. (2003). Cost of lost productive work time among US workers with depression. *JAMA,* 289(23), 3135-3145. doi:DOI 10.1001/jama.289.23.3135

Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in Major Depression: a systematic review of neuroimaging findings. *Biol Mood Anxiety Disord,* 1(1), 10. doi:10.1186/2045-5380-1-10

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. (2017). The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause,* 24(7), 728-753. doi:10.1097/gme.0000000000000921

Tranter, R., Bell, D., Gutting, P., Harmer, C., Healy, D., & Anderson, I. M. (2009). The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. *J Affect Disord,* 118(1-3), 87-93. doi:10.1016/j.jad.2009.01.028

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry,* 161(11), 1957-1966. doi:10.1176/appi.ajp.161.11.1957

Voinov, B., Richie, W. D., & Bailey, R. K. (2013). Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord,* 15(2). doi:10.4088/PCC.12r01468

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., Derijk, R. H., Verhagen, J. C., van Dyck, R., . . . Penninx, B. W. (2009). Major Depressive Disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry,* 66(6), 617-626. doi:10.1001/archgenpsychiatry.2009.50

Weller, E. B., Kloos, A., Kang, J., & Weller, R. A. (2006). Depression in children and adolescents: does gender make a difference? *Curr Psychiatry Rep,* 8, 108-114. doi:10.1007/s11920-006-0007-1

Wessa, M., & Lois, G. (2015). Brain functional effects of psychopharmacological treatment in Major Depression: a focus on neural circuitry of affective

processing. *Current neuropharmacology*, 13(4), 466-479. doi:10.2174/1570159X13666150416224801

Willner, P., Scheel-Kruger, J., & Belzung, C. (2013). The neurobiology of depression and antidepressant action. *Neurosci Biobehav Rev*, 37(10 Pt 1), 2331-2371. doi:10.1016/j.neubiorev.2012.12.007

World Health Organization. (2017). *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization.

Zakzanis, K. K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in Major Depressive Disorder. *Neuropsychiatry Neuropsychol Behav Neurol*, 11(3), 111-119. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9742509

Zuckerman, H., Pan, Z., Park, C., Brietzke, E., Musial, N., Shariq, A. S., . . . McIntyre, R. S. (2018). Recognition and treatment of cognitive dysfunction in Major Depressive Disorder. *Front Psychiatry*, 9, 655. doi:10.3389/fpsyt.2018.00655

Chapter 2

Altered Hippocampal Function with Preserved Cognitive Performance in Treatment Naïve Major Depressive Disorder

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Abstract

Objective: The hippocampus is implicated in the pathophysiology of major depressive disorder, with evidence that morphological changes occur with disease progression. It was hypothesized that treatment naïve patients with depression would show performance deficits in hippocampus-dependent memory trials, with concurrent hippocampal activation deficits on functional magnetic resonance imaging, compared to control participants.

Methods: Thirteen treatment naïve patients with major depressive disorder, and 13 control participants, completed a hippocampus-dependent memory functional magnetic resonance imaging Process Dissociation Task.

Results: On behavioural measures of habit memory and guessing there were no significant differences between groups. Functional magnetic resonance imaging analysis indicated that compared to the control group, the major depressive disorder group showed increased activation in parahippocampal gyrus and hippocampus on habit memory and non-item trials.

Conclusions: These alterations in hippocampal functioning with preserved cognitive performance on a test of hippocampus dependent memory in major depressive disorder may be indicative of a compensatory mechanism.

Key Words: Major Depressive Disorder, Hippocampus, Recollection Memory, Functional Magnetic Resonance Imaging, Episodic Memory

Introduction

Although the precise neural underpinnings of Major Depressive Disorder (MDD) have not been fully elucidated, several lines of evidence suggest the disruption of cortico-limbic networks (Klauser et al., 2015). A recent meta-analysis of resting state functional connectivity has indicated a decrease in connectivity in fronto-parietal systems important for cognitive control, and reduced connectivity between limbic (areas mediating affect) and medial prefrontal cortex regions (important for top down control of emotion regulation) (Kaiser et al., 2015). Meta-analysis of connectivity with seed regions in the default mode network has demonstrated hyperconnectivity between default mode network seeds and dorsolateral prefrontal cortex, and between the hippocampus and the medial prefrontal cortex and middle temporal gyrus in depression (Kaiser et al., 2015). The hippocampus, a key region in these networks, has been strongly implicated in the pathophysiology of MDD.

The hippocampus is a stress sensitive structure that may be affected by changes in the hypothalamic-pituitary-adrenal (HPA) axis, and vice versa. Neurobiological responses to physical and psychological stress are mediated in part by the HPA axis. HPA axis hyperactivity (Pariante & Miller, 2001; Vreeburg et al., 2009) and elevated cortisol levels (Burke et al., 2005; Islam et al., 2018) are consistent finding in studies of MDD. Engagement of the HPA axis prompts the release of glucocorticoids, which help with bodily responses to stress by modulating a number of metabolic functions including pro-inflammatory

responses and the liberation of energy stores (Sapolsky, 2000). The hippocampus contains abundant concentrations of glucocorticoid receptors (De Kloet et al., 1998) and is a major site in the glucocorticoid negative feedback circuitry of the HPA axis (Jacobson & Sapolsky, 1991). However, it has been theorized that chronic or repeated periods of stress can result in elevated glucocorticoid levels, compromised hippocampal function (Diamond et al., 2006) and reductions in hippocampal volume (McEwen, 2000; McEwen & Sapolsky, 1995). Glucocorticoid mediated changes in hippocampal volume are thought to result from inhibition of neurogenesis, dendritic atrophy and impaired glucose metabolism (Gould & Tanapat, 1999; Reagan & McEwen, 1997; Sapolsky, 2000; Tatomir et al., 2014). Stress related reductions in neuroplasticity, including decreased neurogenesis, increased remodeling of dendrites, loss of glial cells, or increased excitotoxicity, could lead to smaller hippocampal volume, disruptions in fronto-temporal circuitry and increased vulnerability to subsequent episodes of depression (McEwen, 1999; Pittenger & Duman, 2008). Hippocampal loss and remodeling and the corresponding loss in glucocorticoid receptor density may lead to inefficacious inhibitory control of the corticotrophin-releasing hormone-producing cells of the hypothalamus, and result in increased availability of glucocorticoids and the cyclic worsening of this cascade (Bremner et al., 2000). However, some MDD patients responding to antidepressants treatment have shown normalization of HPA regulation patterns (Aihara et al., 2007; McKay & Zakzanis, 2010).

The hippocampus has been studied extensively through volumetric Magnetic Resonance Imaging (MRI) (Bora et al., 2012; Koolschijn et al., 2009; McKinnon et al., 2009) and behavioural tasks targeting hippocampal function (Campbell & MacQueen, 2004; Frodl et al., 2006; Shelton & Kirwan, 2013). The largest multi-site data set to date has indicated no differences in hippocampal volume between patients with first episode MDD and controls (Schmaal et al., 2015). Patients with multiple episodes of MDD have demonstrated smaller hippocampal volumes compared to controls (McKinnon et al., 2009; Schmaal et al., 2015; Videbech & Ravnkilde, 2004), as have patients with longer illness duration (McKinnon et al., 2009). MacQueen et al. (2003) demonstrated a logarithmic relationship between hippocampal volume and duration of illness, suggesting emergence of reduction in hippocampal volume early in disease progression, though not prior to first presentation of depression.

Imaging studies of healthy participants have highlighted the importance of hippocampal recruitment for declarative memory. It has been suggested that the hippocampus plays a role in information retrieval success (MacQueen et al., 2003; McKinnon et al., 2009), visual and spatial memory (McEwen, 2004; Sheline et al., 1996), and recollection memory (Brown & Aggleton, 2001; Merkow et al., 2015; Nyberg et al., 1996; Yonelinas, 1997). A review of imaging research on medial temporal lobe memory functions found that the strongest link to hippocampal activation was associated with recollection memory (Diana et al., 2007). Healthy control participants scoring high for depressive symptoms on the

Beck Depression Inventory (BDI) have demonstrated impaired performance on a delayed match to sample test (Becker et al., 2009), a test associated with hippocampal neurogenesis in rodents (Winocur et al., 2006). The groups did not differ on other measures of memory not dependent on hippocampal neurogenesis, suggesting that impaired hippocampal-dependent memory may be a pre-clinical marker for depression (Becker et al., 2009).

Changes in hippocampal integrity that occur with depression are thought to be reflected in changes in hippocampal-dependent memory tasks and there is extensive evidence that people with recurrent depression have impairment in hippocampal-dependent memory, even when euthymic (Campbell & MacQueen, 2004). Whether or not these changes in hippocampal function are present early in the course of depressive illness is less well-established (Fairhall et al., 2010; MacQueen et al., 2003; Werner et al., 2009).

The objective of the present study, therefore, was to assess whether differences in behavioural and neuroimaging measures of hippocampal functioning are present in people with depression presenting for treatment for the first time.

Methods

Participant Selection

Thirteen participants with depression were recruited from the Mood Disorders Program at St. Joseph's Healthcare Hamilton. Thirteen age and sex matched control participants were recruited from the community. The St Joseph's

Healthcare Hamilton Research Ethics Board granted ethical approval. All participants gave written informed consent. Participants with a history of head injury, neurological illness, alcohol or substance abuse, or history of electroconvulsive therapy or transcranial magnetic stimulation within the last two years, were excluded. Controls were free from medication and had no current symptoms or medical history of a mental health disorder. Participants had no past treatment history for MDD, although some participants reported past episodes that had been untreated. Participants with depression met criteria for non-psychotic unipolar MDD as determined by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (First et al., 2002). Mood symptoms were assessed just prior to neuroimaging with the Beck Depression Inventory (BDI; Beck & Beamesderfer, 1974).

Process Dissociation Task:

The Process Dissociation Task (Jacoby, 1998) was adapted for a neuroimaging environment (see Figure 1) as previously described (Milne et al., 2012).

Image Acquisition

Images were acquired on a 3T GE MRI scanner. Participants completed the Process Dissociation Task across 5 fMRI runs, followed by an anatomical scan. Functional images prescribed 13 axial slices (3 mm thickness) centered on the head of the left hippocampus. Blood oxygen-level dependent (BOLD) images were acquired using an echo planar pulse sequence [echo time (TE) = 43 ms; repetition time (TR) = 3000 ms; matrix = 128 × 64; flip angle = 90°. Stimuli were

presented visually according to an event related design with a jittered inter-stimulus interval of 3, 6, or 12 second duration, during which a fixation point was displayed. A 3 second scanner silent period was incorporated after each TR, to allow participants to give verbal responses, which were recorded with an MR-compatible microphone affixed to the head coil. Subsequently, a T1-weighted anatomical scan was obtained; 3D inversion recovery prepped, fast spoiled gradient recalled pulse sequence, sagittal plane, TR = 10.8 ms, TE = 2 ms, inversion time = 400 ms, flip angle= 20°, matrix 256 x 256, field of view = 24, slice thickness 1mm, no skip, 124 contiguous slices.

Analysis

Between group comparisons of age and memory performance were calculated with two-tailed t-tests. Acquired images were preprocessed and analyzed in Brain Voyager QX version 1.10.4 (Brain Innovation; Goebel et al., 2006) (Maastricht, The Netherlands). Functional data sets were slice-time corrected, linear detrended, 3D-motion corrected and realigned, and normalized to Talairach space (Talairach & Tournoux, 1988). High-resolution T1-weighted 3D anatomical scans were transformed into Talairach space and used for coregistration. Regions of interest were prescribed for the hippocampus and parahippocampal gyrus and were inspected and confirmed by a second tracer (GBCH).

An event related model was used to examine the BOLD signal at every voxel. Data were analyzed using a random-effects multiple general linear model. Recollection memory, habit memory, non-item, and study list presentations were

set as the explanatory variables accounting for differences in BOLD signal within and between groups. Contrasts were corrected for multiple-comparisons using a false discovery rate (FDR) of 0.05. The average statistical value for the resulting regions of interest (ROIs) are reported.

Results

Demographics

Demographic information for participants is listed in Table 1. The MDD group had a mean illness duration of 4.7 ± 3.5 years, mean of 2.6 ± 2.4 episodes, and a mean BDI score of 27.5 ± 10.5. MRI scans were scheduled as close to the clinical assessment as possible. As a result, 3 MDD participants had commenced with antidepressant treatment 6, 4 and 2 days respectively, prior to scanning. One MDD participant was receiving an antipsychotic. All other MDD participants had no lifetime history of exposure to any psychotropic medications.

Memory Performance

There were no differences in recollection memory performance between MDD patients and controls. The MDD group also performed similarly to controls on both habit memory trials and in their tendency to guess on non-item trials (see Table 2).

Imaging Results

ROI analyses were conducted to examine hippocampal engagement in response to task conditions. ROIs were manually traced on a summed co-registered anatomical image at the group level to include the hippocampus bilaterally.

Between group activation patterns were determined for the contrast of each type of memory trial (recollection, habit and non-item trials) against the presentation of the study list (See Table 3).

MDD patients had significantly increased bilateral activation of the hippocampus during habit memory trials compared to controls. In addition, MDD patients showed heightened activation of the parahippocampal gyrus bilaterally during non-item trials in comparison to controls. For the comparison of recollection memory trials versus the study list, MDD patients also showed greater bilateral parahippocampal gyrus (Brodmann areas 36 & 27) activation than controls, although these results did not survive correction for multiple comparisons (see Figure 2). Given the memory performance results, it appears that to perform at equitable levels on the process dissociation task, MDD patients showed heightened activation broadly across all three memory domains.

Discussion

We report findings of heightened hippocampal and parahippocampal activation during habit memory and non-item trials in a group of recently diagnosed patients with MDD, without corresponding impairments in hippocampus-dependent memory compared to a matched control group. Furthermore, greater recruitment of the hippocampus was observed in the MDD group during recollection memory trials in comparisons to the control group, though this did not survive correction for multiple comparisons. The current results support previous findings of altered hippocampal function in MDD. In a previous study examining process

dissociation memory in participants with a lengthy MDD history (mean number of episodes 5.6 ± 2.4, with mean illness duration in years of 20.1 ± 12.8) patients with MDD scored significantly lower on recollection and habit trials, when compared to controls (Milne et al., 2012). There was increased activation in left parahippocampal and right hippocampal gyri in the healthy controls compared to patients with MDD during recollection memory trials, with no significant between group differences on habit or non-item trials. These results suggest that at the onset of MDD, there is a broad heightened engagement of the hippocampus across trial types in response to task demands. Similarly, an fMRI study of unmedicated MDD patients and healthy controls performing a Stroop task found no between group differences in reaction time or accuracy (Wagner et al., 2006). However, compared to controls, in the interference condition MDD patients demonstrated increased activity in the left dorsolateral prefrontal cortex and in rostral anterior cingulate gyrus, in addition to patterns of activity in the dorsal anterior cingulate gyrus that were similar to the controls, suggesting recruitment of additional resources was necessary for the MDD group to perform similarly to the healthy controls. It is possible that hippocampal functioning follows a trajectory as MDD progresses, where in the early stages changes in function play a compensatory role, but across time there is a worsening of memory function and performance (Milne et al., 2012). In contrast, healthy controls differentially recruit the hippocampus during recollection memory trials compared to habit or non-item trials.

Greater activation across trial type in MDD patients may suggest that in the early course of MDD patients are able to successfully complete the task and compensate with increased hippocampal recruitment. However, with a protracted course of illness consisting of repeated depressive episodes and corresponding prolonged exposures to glucocorticoids (Campbell et al., 2004; Videbech & Ravnkilde, 2004), hippocampal recruitment may be compromised. In related work examining brain proton magnetic resonance spectroscopy (Milne et al., 2009) we have associated reduced hippocampal volumes in patients with multiple MDD episodes with elevated hippocampal choline levels. As choline is considered a marker of neuronal membrane turnover (Klein, 2000), elevated levels may reflect stress reactive remodeling processes in the hippocampus. Milne et al. (2009) further reported an absence of hippocampal volume loss in MDD patients that was accompanied by increased levels of myo-inositol. These findings suggest that early in the course of MDD there may be increases in glial cell density at the hippocampus (Milne et al., 2009). In the context of the current study, it is interesting to speculate that if the heightened hippocampal engagement in MDD patients reflects some kind of compensatory processes, then the associated increases in local metabolic needs may be satisfied by changes in the density or recruitment of glia (Alberini et al., 2018; Takata et al., 2018).

Werner et al. (2009) used fMRI to examine hippocampus related memory in MDD, applying a subthreshold paired associate task using faces and occupations that failed to differentiate hippocampal activation between MDD

patients and controls. Group differences in other regions associated with memory, including frontal and parietal regions, were observed. The lack of differences in the hippocampus might suggest that the task employed was insufficiently sensitive to hippocampal activation changes, to isolate group differences in this region. Werner et al. (2009) postulated that the small sample size and relatively young age of patients with depression may have contributed to their lack of findings in the hippocampus. These findings may be contrasted with Fairhall et al. (2010), using an associative encoding task in MDD patients (first and recurrent episode, medicated and non-medicated) and healthy controls, cognitively, there were no between group differences on task performance. Functionally, MDD participants did not display the same heightened hippocampus fMRI activation in response to successful encoding the control group did, but rather an increased activation in intraparietal sulcus. This suggests a breakdown or dysregulation of memory-related hippocampus function on a memory task and possible compensatory mechanisms, rather than an up or down regulation in activation (Fairhall et al., 2010). Imaging studies have found that while MDD patients may engage additional neural resources in response to task demands, there may not be an accompanying improvement in task performance (Herwig et al., 2010; Zhou et al., 2010).

The present study has some limitations, the modest sample size being the most obvious. Further, our focus solely on the hippocampus means that possible compensatory recruitment of additional brain regions could not be resolved.

Furthermore, although standard hand tracing protocols exist for disambiguating the anterior portion of the hippocampus from the amygdala (Boccardi et al., 2011; Yucel et al., 2008) it remains possible that activation patterns included contributions from the amygdala due to partial volume effects.

In summary, young adults presenting for first treatment of MDD did not demonstrate recollection memory deficits during a hippocampus dependent memory task. Instead, MDD patients showed heightened hippocampal activation without corresponding memory deficits on all memory trial types. These findings provide complementary fMRI evidence that the hippocampus is a region sensitive to the impact of disease burden. A longitudinal repeated-measures study of changes in habit memory and concurrent changes in hippocampal volume and integrity or hippocampal functional activation would be a positive contribution to understanding the evolution of hippocampal changes in the progression of MDD.

Tables and Figures

Table 1. Demographic and clinical information for MDD patients and healthy control participants

	MDD Group	Control Group	Statistics
N	13	13	-
Female (%)	5 (39%)	7 (54%)	$X^2(1, N=26) = .619, p = .431$
Age in years	25.8 ± 7.5	27.2 ± 7.9	$t(24) = -.435, p = .667, d = -0.18$
Education in years	13.2 ± 1.5†	17.9 ± 3.0	$t(21) = -4.535, p = <.0005, d = -1.86$
BDI	27.5 ± 10.5	1.6 ± 2.3	$t(13.167) = 8.652, p = <.0005, d = 3.53$
Illness Duration	4.7 ± 3.5‡	NA	-
Number of Episodes	2.6 ± 2.4†	NA	-

† Data missing for 3 participants. ‡ Data missing for 5 participants.

Note: Data are presented as Mean ± SD unless otherwise noted.

Table 2. Memory performance across trial type during the process dissociation task

Trial Type	MDD Group	Control Group	Statistics
Recollection	0.72 ± (0.11)	0.67 (0.18)	$t(24) = 0.846$, $p = 0.406$, $d = 0.35$
Habit	0.42 ± (0.20)	0.36 (0.18)	$t(24) = 0.773$, $p = 0.447$, $d = 0.32$
Guessing	0.61 ± (0.09)	0.60 (0.11)	$t(24) = 0.019$, $p = 0.985$, $d = 0.01$

Table 3. Memory-related fMRI activation identified in between group comparisons

Trial Type	MNI Coordinates			Region	BA	t-value	d	Cluster size (voxels)
	x	y	z					
Recollection – Study Trials								
MDD > Control	24	-43	-6	Parahippocampal gyrus	36	3.165	1.29	177†
	-22	-34	-3	Parahippocampal gyrus	27	3.224	1.32	918†
Habit – Study Trials								
MDD > Control	27	-31	-4	Hippocampus		3.268	1.33	2431
	-19	-34	-2	Hippocampus/ Parahippocampal gyrus	27	3.477	1.42	2394
Non-item – Study Trials								
MDD > Control	24	30	-3	Parahippocampal gyrus	27	3.161	1.29	713
	-22	-33	-3	Hippocampus/ Parahippocampal gyrus	27	3.660	1.49	2547

† Results not corrected for multiple comparisons.

BA = Brodmann Area

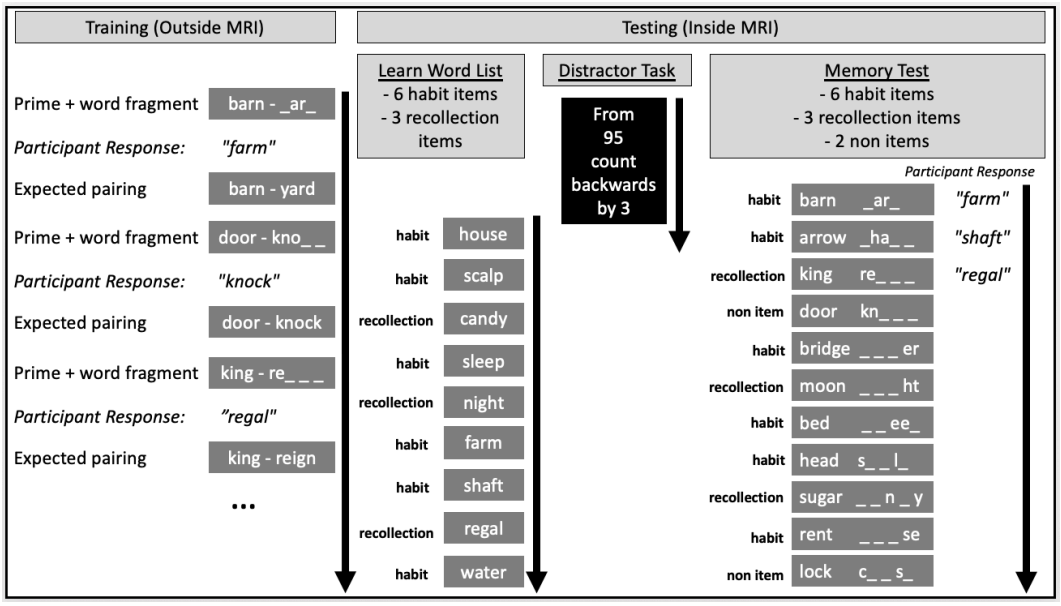

Figure 1: Schematic representation of the process dissociation task.

Training phase: participants were repeatedly exposed to eighteen stimulus words pairs. Each word that appeared on the left side of the screen was paired with one of two possible associative responses that occur with equal frequency in published norms (e.g. mountain-high, mountain-hill). Participants were given two seconds to guess the correct answer to complete the word fragment (e.g. mountain hill or mountain high) before the correct completed word pair combination appeared on the screen. Testing phase: participants were presented with 17 test blocks each consisting of presentation of a study list, an arithmetic distractor task and then completion of a memory test. Participants were instructed to respond verbally and complete the word fragments with words in the immediately preceding study list, or to provide their best guess if they could not remember which word was presented in the study list.

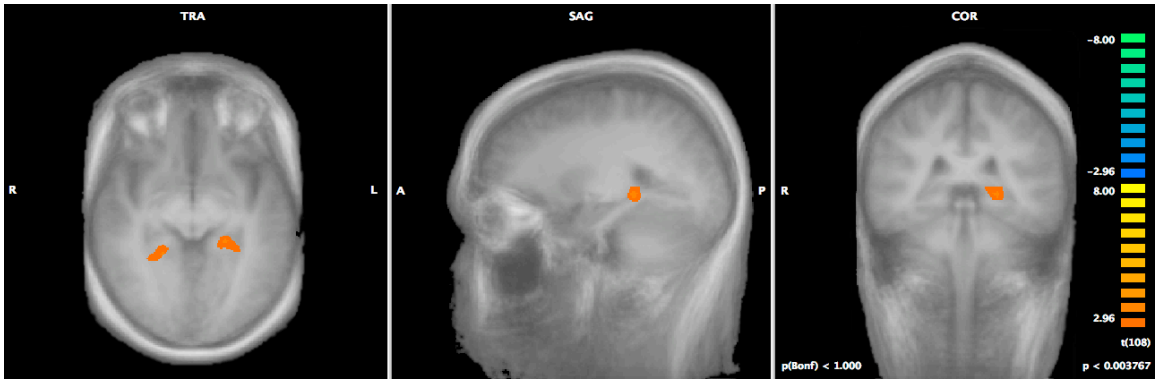

Figure 2. Group differences in hippocampal activation during recollection memory trials.

MDD patients show a trend towards heightened left (t = 3.165) and right (t = 3.224) parahippocampal activation compared to healthy control participants. Statistical maps are superimposed on averaged anatomical group images. Images are presented according to radiological convention. Results are not FDR corrected.

References

Aihara, M., Ida, I., Yuuki, N., Oshima, A., Kumano, H., Takahashi, K., . . . Mikuni, M. (2007). HPA axis dysfunction in unmedicated Major Depressive Disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. *Psychiatry Res,* 155(3), 245-256. doi:10.1016/j.pscychresns.2006.11.002

Alberini, C. M., Cruz, E., Descalzi, G., Bessieres, B., & Gao, V. (2018). Astrocyte glycogen and lactate: New insights into learning and memory mechanisms. *Glia,* 66(6), 1244-1262. doi:10.1002/glia.23250

Beck, A. T., & Beamesderfer, A. (1974). Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry,* 7(0), 151-169. doi:10.1159/000395074

Becker, S., MacQueen, G. M., & Wojtowicz, J. M. (2009). Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: effects of interference, stress and depression. *Brain Res,* 1299, 45-54. doi:10.1016/j.brainres.2009.07.095

Boccardi, M., Ganzola, R., Bocchetta, M., Pievani, M., Redolfi, A., Bartzokis, G., . . . Frisoni, G. B. (2011). Survey of protocols for the manual segmentation of the hippocampus: preparatory steps towards a joint EADC-ADNI harmonized protocol. *J Alzheimers Dis,* 26 Suppl 3, 61-75. doi:10.3233/JAD-2011-0004

Bora, E., Fornito, A., Pantelis, C., & Yücel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord,* 138(1-2), 9-18. doi:10.1016/j.jad.2011.03.049

Brain Innovation. BrainVoyager QX (Version 1.10.4). Maastricht, The Netherlands: Brain Innovation.

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in Major Depression. *Am J Psychiatry,* 157(1), 115-118. doi:10.1176/ajp.157.1.115

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci,* 2(1), 51-61. doi:10.1038/35049064

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

Campbell, S., & MacQueen, G. M. (2004). The role of the hippocampus in the pathophysiology of Major Depression. *J Psychiatry Neurosci,* 29(6), 417-426. Retrieved from /pmc/articles/PMC524959/?report=abstract

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: A meta-analysis. *Am J Psychiatry,* 161(4), 598-607. doi:10.1176/appi.ajp.161.4.598

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocr Reviews,* 19(3), 269-301. doi:10.1210/edrv.19.3.0331

Diamond, D. M., Campbell, A. M., Park, C. R., Woodson, J. C., Conrad, C. D., Bachstetter, A. D., & Mervis, R. F. (2006). Influence of predator stress on the consolidation versus retrieval of long-term spatial memory and hippocampal spinogenesis. *Hippocampus,* 16(7), 571-576. doi:10.1002/hipo.20188

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn Sci,* 11(9), 379-386. doi:10.1016/j.tics.2007.08.001

Fairhall, S. L., Sharma, S., Magnusson, J., & Murphy, B. (2010). Memory related dysregulation of hippocampal function in Major Depressive Disorder. *Biol Psychiatry,* 85(3), 499-503. doi:10.1016/j.biopsycho.2010.09.002

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)* New York: Biometrics Research, New York State Psychiatric Institute.

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., . . . Meisenzahl, E. M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in Major Depression. *J Psychiatry Neurosci,* 31(5), 316-323. Retrieved from http://linkinghub.elsevier.com/retrieve/pii/S0006899314017107

Goebel, R., Esposito, F., & Formisano, E. (2006). Analysis of functional image analysis content (FIAC) data with Brainvoyager QX: From single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Hum Brain Mapp,* 27, 392-401. doi:10.1002/hbm.20249

Gould, E., & Tanapat, P. (1999). Stress and hippocampal neurogenesis. *Biol Psychiatry,* 46(11), 1472-1479. doi:10.1016/S0006-3223(99)00247-4

Herwig, U., Bruhl, A. B., Kaffenberger, T., Baumgartner, T., Boeker, H., & Jancke, L. (2010). Neural correlates of 'pessimistic' attitude in depression. *Psychol Med,* 40(5), 789-800. doi:10.1017/S0033291709991073

Islam, M., Islam, M., Ahmed, I., Moktadir, A., Nahar, Z., Islam, M., . . . Hasnat, A. (2018). Elevated serum levels of malondialdehyde and cortisol are associated with major depressive disorder: A case-control study. *SAGE Open Medicine,* 6, 1-7. doi:10.1177/2050312118773953

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Reviews,* 12(2), 118-134. doi:10.1210/edrv-12-2-118

Jacoby, L. L. (1998). Invariance in automatic influences of memory: toward a user's guide for the process-dissociation procedure. *J Exp Psychol Learn Mem Cogn,* 24(1), 3-26. doi:10.1037/0278-7393.24.1.3

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-Scale network dysfunction in Major Depressive Disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry,* 72(6), 603-611. doi:10.1001/jamapsychiatry.2015.0071

Klauser, P., Fornito, A., Lorenzetti, V., Davey, C. G., Dwyer, D. B., Allen, N. B., & Yucel, M. (2015). Cortico-limbic network abnormalities in individuals with current and past Major Depressive Disorder. *J Affective Disord,* 173, 45-52. doi:10.1016/j.jad.2014.10.041

Klein, J. (2000). Membrane breakdown in acute and chronic neurodegeneration: focus on choline-containing phospholipids. *J Neural Transm (Vienna),* 107(8-9), 1027-1063. doi:10.1007/s007020070051

Koolschijn, P. C. M. P., van Haren, N. E. M., Lensvelt-Mulders, G. J. L. M., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in Major Depressive Disorder: a meta-analysis of magnetic resonance

imaging studies. *Hum Brain Mapp,* 30(11), 3719-3735. doi:10.1002/hbm.20801

MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., . . . Young, L. T. (2003). Course of illness, hippocampal function, and hippocampal volume in Major Depression. *Proc Natl Acad Sci USA,* 100(3), 1387-1392. doi:10.1073/pnas.0337481100

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annu Rev Neurosci,* 22(1), 105-122. doi:10.1146/annurev.neuro.22.1.105

McEwen, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biol Psychiatry,* 48(8), 721-731. doi:10.1016/S0006-3223(00)00964-1

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci,* 1032(1), 1-7. doi:10.1196/annals.1314.001

McEwen, B. S., & Sapolsky, R. M. (1995). Stress and cognitive function. *Curr Opin Neurobiology,* 5(2), 205-216. doi:10.1016/0959-4388(95)80028-X

McKay, M. S., & Zakzanis, K. K. (2010). The impact of treatment on HPA axis activity in unipolar major depression. *J Psychiatr Res,* 44(3), 183-192. doi:10.1016/j.jpsychires.2009.07.012

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with Major Depressive Disorder. *J Psychiatry Neurosci,* 34(1), 41-54. Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19125212&retmode=ref&cmd=prlinks

Merkow, M. B., Burke, J. F., & Kahan, M. J. (2015). The human hippocampus contributes to both the recollection and familiarity components of recognition memory. *Proc Natl Acad Sci USA,* 112(46), 14378 - 14383. doi:10.1073/pnas.1513145112

Milne, A. M., MacQueen, G. M., & Hall, G. B. (2012). Abnormal hippocampal activation in patients with extensive history of Major Depression: an fMRI study. *J Psychiatry Neurosci,* 37(1), 28-36. doi:10.1503/jpn.110004

Milne, A. M., MacQueen, G. M., Yucel, K., Soreni, N., & Hall, G. B. (2009). Hippocampal metabolic abnormalities at first onset and with recurrent episodes of a Major Depressive Disorder: a proton magnetic resonance spectroscopy study. *Neuroimage,* 47(1), 36-41. doi:10.1016/j.neuroimage.2009.03.031

Nyberg, L., McIntosh, A. R., Cabeza, R., Habib, R., Houle, S., & Tulving, E. (1996). General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc Natl Acad Sci USA,* 93(20), 11280-11285. doi:10.1073/pnas.93.20.11280

Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in Major Depression: relevance to pathophysiology and treatment. *Biol Psychiatry,* 49(5), 391-404. doi:10.1016/S0006-3223(00)01088-X

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology,* 33(1), 88-109. doi:10.1038/sj.npp.1301574

Reagan, L. P., & McEwen, B. S. (1997). Controversies surrounding glucocorticoid-mediated cell death in the hippocampus. *J Chem Neuroanat,* 13(3), 149-167. doi:10.1016/S0891-0618(97)00031-8

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry,* 57(10), 925-935. doi:10.1001/archpsyc.57.10.925

Schmaal, L., Veltman, D. J., van Erp, T. G., Samann, P. G., Frodl, T., Jahanshad, N., . . . Hibar, D. P. (2015). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry,* 21(6), 806-812. doi:10.1038/mp.2015.69

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent Major Depression. *Proc Natl Acad Sci USA,* 93(9), 3908-3913. doi:10.1073/pnas.93.9.3908

Shelton, D. J., & Kirwan, C. B. (2013). A possible negative influence of depression on the ability to overcome memory interference. *Behav Brain Research,* 256, 20-26. doi:10.1016/j.bbr.2013.08.016

Takata, N., Sugiura, Y., Yoshida, K., Koizumi, M., Hiroshi, N., Honda, K., . . . Tanaka, K. F. (2018). Optogenetic astrocyte activation evokes BOLD

fMRI response with oxygen consumption without neuronal activity modulation. *Glia*. doi:10.1002/glia.23454

Talairach, J., & Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain. In *3-dimensional Proportional System: An Approach to Cerebral Imaging* (pp. 122). Stuttgart: George Thieme Verlag.

Tatomir, A., Micu, C., & Crivii, C. (2014). The impact of stress and glucocorticoids on memory. *Clujul Med,* 87(1), 3-6. doi:10.15386/cjm.2014.8872.871.at1cm2

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry,* 161(11), 1957-1966. doi:10.1176/appi.ajp.161.11.1957

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., Derijk, R. H., Verhagen, J. C., van Dyck, R., . . . Penninx, B. W. (2009). Major Depressive Disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry,* 66(6), 617-626. doi:10.1001/archgenpsychiatry.2009.50

Wagner, G., Sinsel, E., Sobanski, T., Kohler, S., Marinou, V., Mentzel, H. J., . . . Schlosser, R. G. (2006). Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. *Biol Psychiatry,* 59(10), 958-965. doi:10.1016/j.biopsych.2005.10.025

Werner, N. S., Meindl, T., Materne, J., Engel, R. R., Huber, D., Riedel, M., . . . Hennig-Fast, K. (2009). Functional MRI study of memory-related brain regions in patients with depressive disorder. *J Affect Disord,* 119(1-3), 124-131. doi:10.1016/j.jad.2009.03.003

Winocur, G., Wojtowicz, J. M., Sekeres, M., Snyder, J. S., & Wang, S. (2006). Inhibition of neurogenesis interferes with hippocampus-dependent memory function. *Hippocampus,* 16(3), 296-304. doi:10.1002/hipo.20163

Yonelinas, A. P. (1997). Recognition memory ROCs for item and associative information: the contribution of recollection and familiarity. *Memory Cognit,* 25(6), 747-763. doi:10.3758/BF03211318

Yucel, K., Taylor, V. H., McKinnon, M. C., Macdonald, K., Alda, M., Young, L. T., & MacQueen, G. M. (2008). Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology,* 33(2), 361-367. doi:10.1038/sj.npp.1301405

Zhou, Y., Yu, C., Zheng, H., Liu, Y., Song, M., Qin, W., . . . Jiang, T. (2010). Increased neural resources recruitment in the intrinsic organization in Major Depression. *J Affect Disord,* 121(3), 220-230. doi:10.1016/j.jad.2009.05.029

Chapter 3

Differential Effects of Acute Tryptophan Depletion on Emotional Stroop in Midlife Women Receiving Estrogen-based Treatment: An fMRI Study

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Abstract

Introduction: Estrogen fluctuations may lead to changes in the serotonergic system and influence menopause transition-related mood symptoms. Serotonin availability can be temporarily manipulated through the acute tryptophan depletion paradigm. We examine the effect of acute tryptophan depletion on mood and emotion recognition in midlife women receiving estradiol treatment.

Methods: In a crossover design, 14 midlife women (age range 45 to 60 years) receiving estradiol were assigned to acute tryptophan depletion or sham and completed a functional magnetic resonance imaging Emotional Conflict Task.

Results: In both conditions, participants demonstrated emotional Stroop in reaction time. Incongruent adaptation in accuracy was observed in Sham condition, and in reaction time in the acute tryptophan depletion condition. There was lower brain blood oxygen level dependent activity in acute tryptophan depletion compared to Sham in the incongruent adaptation condition in bilateral angular gyrus, right lateral occipital cortex, and left middle temporal gyrus. Greater brain blood oxygen level dependent activity was observed in acute tryptophan depletion in the emotional Stroop condition, in regions including left superior parietal lobule extending to the precuneus and posterior cingulate gyrus.

Conclusions: Acute tryptophan depletion in estrogen users attenuates incongruent adaptation in terms of accuracy. Brain blood oxygen level dependent activity was reduced in acute tryptophan depletion compared to Sham in the incongruent adaptation condition and increased in the emotional Stroop condition. The high

dose of estradiol women were receiving may have been sufficient to maintain serotonin homeostasis, preventing women experiencing a rapid deterioration of mood or an increase of vasomotor symptoms during acute tryptophan depletion.

Key Words: acute tryptophan depletion, perimenopause, emotional conflict task, emotional Stroop

Introduction

Women are at higher risk to develop Major Depressive Disorder (MDD) across the lifespan, with a 5.1% prevalence compared to 3.6% in men (World Health Organization, 2017). Worldwide, MDD has already become the source of primary disease burden in women (World Health Organization, 2008). It has been postulated that the heightened risk for developing mood symptoms among women could be at least in part related to intervals of greater hormonal fluctuations across the lifespan, i.e., hormone-related windows of vulnerability (Steiner, 2003; Soares and Zitek, 2008). Hormonal fluctuations are commonly observed during reproductive years, occurring periodically in the luteal phase of the menstrual cycle (Hantsoo and Epperson, 2015), and during postpartum periods (Marcus, 2009). Fluctuations in the hormonal milieu are also a characteristic of the menopausal transition (Bromberger and Epperson, 2018). The menopausal transition is characterized by vasomotor symptoms, changes in sleep, vaginal dryness, dyspareunia, and increased symptoms of depression and anxiety (Santoro, 2016). The multi-site community-based prospective Study of Women's Health Across the Nation confirmed a heightened vulnerability for depression while examining aging and the transition to menopause across a 13-year follow up during midlife years; women with no history of MDD have a 28% greater risk of developing MDD during the menopause transition, whereas women with a lifetime history of MDD have a 59% increased risk of experiencing a recurrent MDD episode (Bromberger et al., 2015). Even midlife women without a history

of depression were twice as likely to develop depressive symptoms compared to an age-matched premenopausal control group (Cohen et al., 2006). The risk for developing depression appears to be higher during and after perimenopause as compared to pre-menopause (Cohen et al., 2006; Bromberger et al., 2011). Increased risk for MDD recurrence or onset in perimenopause has also been identified in women with a history of severe premenstrual mood symptoms, or who are experiencing poor sleep, or hot flashes (Freeman et al., 2004).

Overall, women experiencing onset of a major depressive episode during perimenopausal years are more likely to have a lifetime history of MDD, rather than experiencing a new onset of MDD (Maki et al., 2018). This increased risk is not primarily driven by aging (Bromberger and Epperson, 2018), as risk for developing depression diminishes over time – i.e. during late postmenopausal years (Bromberger et al., 2011; Freeman et al., 2014). Recent research has suggested that greater duration of exposure to estrogen, expressed as the length of time from menarche to the initiation of the menopausal transition, may reduce risk of developing depressive symptoms during and up to 10 years after the menopausal transition (Georgakis et al., 2016; Marsh et al., 2017). Similar protective effects have been reported for women with a history of using oral contraceptives, perhaps due to the fact that oral contraceptives act to reduce fluctuations in the hormonal milieu, and provide a steady exposure to changes in endogenous estrogen (Marsh et al., 2017). In sum, while most women will not encounter depression during the menopausal transition, perimenopause represents

a window of vulnerability during which a subset of women with or without lifetime history of MDD may have an increased risk of developing mood symptoms during a time of intense hormonal fluctuations (Maki et al., 2018).

During menopause transition, hormone therapy (HT) is the standard treatment for vasomotor symptoms, premature hypoestrogenism, genitourinary symptoms, and the prevention of bone loss (The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Several studies have demonstrated that perimenopausal women receiving treatment with transdermal 17 β Estradiol estrogen treatment (ET) have experienced a reduction in depressive symptoms (Schmidt et al., 2000; Soares et al., 2001; Gordon and Girdler, 2014). However, this benefit of ET does not extend to women in the postmenopausal phase (Morrison et al., 2004; Gordon and Girdler, 2014), suggesting that ET provides the most benefit in women in the perimenopausal phase, when hormone levels are fluctuating at a greater intensity.

A recent study examined whether HT could prevent the onset of depressive symptoms in perimenopausal and postmenopausal women (Gordon et al., 2018). In a double-blind, placebo-controlled trial, women received transdermal estradiol (0.1 mg/d) or placebo for 12 months, with oral micronized progesterone (200 mg/d for 12 days) or matched placebo given every 3 months for those in active treatment or placebo, respectively. Women assigned to placebo were more likely to develop depressive symptoms over time compared to women on HT (32.3 % versus 17.3%, OR=2.5; 95% CI, 1.1-5.7, P=.03). The study

suggested that some women could benefit from estrogen-based therapy to mitigate the risks of developing depression.

ET may help to improve mood symptoms by influencing availability of serotonin, a neurotransmitter involved in the regulation of mood and cognition (Lokuge et al., 2011). Estrogen can boost serotonin synthesis and transport (Smith et al., 2004), reduce serotonin degradation (Bethea et al., 2002), increase the availability of post-synaptic serotonin receptor ($5HT_{2A}$) binding sites (Moses-Kolko, 2003), and reduce sensitivity of the presynaptic serotonin autoreceptor ($5HT_{1A}$) (Henderson and Bethea, 2008). Therefore, the interplay between serotonergic neurotransmission and estrogen may have a modulatory role in thermoregulation and in mood.

To assess the effects of reduced serotonin availability in the brain, neural serotonin levels can be temporarily reduced with exposure to the acute tryptophan depletion (ATD) paradigm. Tryptophan is an essential amino acid that is the sole precursor for serotonin synthesis (Richard et al., 2009; Fernstrom et al., 2013) and the rate-limiting step in serotonin production (Schaechter and Wurtman, 1990). Blood plasma tryptophan availability in the brain is determined by a combination of bioavailable tryptophan ingested through consumption of food and the uptake of tryptophan during protein synthesis (Richard et al., 2009). Generally, ATD in healthy participants without a family history of MDD, does not result in a significant change in mood (Fusar-Poli et al., 2006). Women may be more prone to experience mood-diminishing effects of ATD (Menkes et al., 1994; Ellenbogen

et al., 1996; Booij et al., 2002), due to sex differences in serotonin synthesis (Okazawa et al., 2000) and in binding potentials at the serotonin transporter, and $5HT_{1A}$ receptor (Jovanovic et al., 2008). Nevertheless, ATD did not result in increased depressive mood symptoms in euthymic menopausal women with a recent episode of major depression (Epperson et al., 2007), or in non-depressed menopausal or post-menopausal women before or after receiving ET (Epperson et al., 2012; Shanmugan et al., 2017). Reducing serotonin availability in the brain of perimenopausal women allows for the study of serotonergic influence on processing of emotional stimuli, without the confounding factor of low mood (Beacher et al., 2011) that accompanies chronic lowering of serotonin levels, as is hypothesized to be the case in MDD (Baranyi et al., 2017).

The Emotional Conflict Task, an emotional Stroop test paradigm (Etkin et al., 2006; Wortinger et al., 2017) involves presentation of a series of faces with either a fearful or happy facial expression, with the name of a congruent or incongruent emotion overlaid on the face. Participants are required to identify the emotion expressed on the face (task relevant emotional information) while ignoring the name of the emotion printed on the face (task irrelevant emotional information). In healthy comparison participants, an incongruent adaptation effect occurs when reaction time (RT) is decreased and accuracy is increased on an incongruent trial preceded by an incongruent (iI) trial, compared to an incongruent trial preceded by a congruent (cI) trial (Etkin et al., 2006). In both instances, the incongruent trial requires the same cognitive response to the facial

emotion and inhibition of response to the printed name of an emotion. The conflict introduced in the first incongruent presentation of an iI trial enhances the behavioural response to the second incongruent trial (Etkin et al., 2006; Etkin and Schatzberg, 2011).

Using the Emotional Conflict Task, we have shown that menopausal women not receiving HT displayed increased brain blood oxygen level dependent (BOLD) activity in measures of incongruent adaptation including anterior insula, posterior cingulate cortex, inferior and superior parietal lobules, middle and superior temporal gyrus, caudate and putamen (Frey et al., 2010). However, behavioural differences were not observed, suggesting changes in processing of emotional stimuli in women transitioning into menopause. Given the positive effects of selective serotonin reuptake inhibitors on mood, we expect that ATD in a perimenopausal group of mid-life women may negatively affect processing of emotional stimuli in the Emotional Conflict Task, compared to Sham.

The objective of this study was to examine the modulatory effect of ET on mood through its interaction with the serotonergic system in perimenopausal women receiving ET. We utilized a functional magnetic resonance imaging (fMRI) Emotional Conflict Task to examine whether disruption of serotonin production through ATD would disrupt the effects of ET on mood and on processing of emotion information. It was hypothesized that ATD in a group of midlife women with depressive symptoms and receiving ET would not significantly increase mood symptoms (Epperson et al., 2012; Shanmugan et al.,

2017), assuming that the effects of ET on mood are not solely mediated by serotonin. Changes in vasomotor symptoms were also not expected with ATD, as treatment with the serotonin precursor 5-hydroxytryptophan does not significantly reduce the frequency of menopausal hot flashes (Freedman, 2010) and that the effects of ET on thermoregulation may in fact be mediated by other monoamines such as noradrenaline.

Methods

Participants

Twenty-eight female participants were recruited through internet and local advertisements. Prospective participants completed a telephone screening interview. The Research Ethics Board of St. Joseph's Healthcare Hamilton and McMaster University approved the study protocol (REB Project #: 10-3337) and the study was carried out in accordance with the standards provided by the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans TCPS 2 (Canadian Institutes of Health Research et al., December 2014).

Inclusion criteria were women aged 40 to 60 years old in either menopausal transition or early postmenopausal staging as defined by the following Stages of Reproductive Aging Workshop (STRAW; Soules et al., 2001; Harlow et al., 2012) criteria: ≥ 7 day change in menstrual cycle duration (early menopausal transition), ≥ 2 missed menstrual cycles plus at least one ≥ 60 days inter-menstrual interval (late menopausal transition) or ≤ 5 years since last menstrual period (early post-menopause). Additional inclusion criteria were

symptoms of anxiety or depression meeting criteria for MDD on the Mini-International Neuropsychiatric Interview – structured psychiatric diagnostic interview (MINI; Sheehan et al., 1998) or the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) with a score of greater ≥ 20, and menopausal symptoms identified by a total score on the Greene Climacteric Scale (GCS; Greene, 1998) of ≥ 16 and GCS – vasomotor symptom sub score of ≥ 3.

Exclusion criteria were contraindications for HT or for MRI; regular treatment with a selective serotonin reuptake inhibitor, tricyclic antidepressants, mood stabilizers, oral or depot neuroleptics within 12 weeks prior to screening visit, sedatives, hypnotics, or over-the-counter products recognized to affect mood within 8 weeks prior to screening visit; use of psychotropic medication (except ET), herbal supplements or over-the-counter agents known to affect menopausal symptoms, within 8 weeks prior to screening visit, exposure to electroconvulsive therapy in the previous 12 weeks; serious medical diagnoses including thyroid disease, heart disease (angina heart, attack), pulmonary disease, blood or bleeding disease, liver disease, kidney disease, gastrointestinal disease (e.g. ulcers, bleeding, metabolic), epilepsy or seizure, head injury, cancer, human immunodeficiency virus, or acquired immune deficiency syndrome.

Screening Visit

At the in-person pre-intervention screening visit at St. Joseph's Centre for Integrated Healthcare, participants completed a series of questionnaires to

determine study eligibility, including: The MINI (Sheehan et al., 1998); the MADRS (Montgomery and Åsberg, 1979) – a 10 item clinician administered scale assessing current mood symptoms and based on information gleaned during a clinical interview; Profile of Mood States (POMS; Pollock et al., 1979) – a 65 item clinician administered measure of mood states in the previous week, with subscales assessing depression, anger, tension, confusion, vigor and fatigue; the GCS (Greene, 1998) – a 21 item subjective measure of current vasomotor, physical and psychological symptoms associated with Menopause; and the Hot Flash Related Daily Interference Scale (HFRDIS) (Carpenter, 2001) – a 10 item subjective measure of the influence of hot flashes on quality of life in the past week. Participants with STRAW stages +1a, +1b, and +1c were included in the study.

Eligible participants were provided with a study description and provided written informed consent. Participants received financial compensation for study participation.

A blood sample was taken at the screening visit to assess estrogen levels. Blood serum estrogen levels were analyzed using a standard enzyme-linked immunosorbent assay.

Treatment

The treatment phase was initiated with a visit with the study gynecologist, and ET began within 7-10 days of the screening visit. Participants were provided with instructions on how to apply the 17 β-estradiol (100 μg) transdermal patches.

Adverse events, alterations in menopause-related symptoms, and mood changes (POMS and MADRS scores) were monitored 1, 2, 4, and 8 weeks following the initiation of treatment. After 8 weeks of treatment, blood samples were acquired to re-assess levels of follicle stimulating hormone, luteinizing hormone, and estrogen (ET adherence was set at serum estrogen levels > 0.15 nmol/L). Participants responding to ET (defined as ≥ 50% decrease in MADRS scores from baseline screening visit to 8 weeks of treatment) were eligible for inclusion. Moreover, upon completion of the study, and after a maximum of 12 weeks of receiving ET, women with intact uteri received oral micronized progesterone 100-200 mg/day for 14 days to provide endometrial protection (Stute et al., 2016). All participants received appropriate follow-up care with the study psychiatrist and study gynecologist after treatment completion or at study discontinuation.

ATD Procedure

The ATD and Sham depletion conditions were completed at least 7 days apart in a randomized (within subject) assignment. Participants were provided with specific instructions to adhere to a low-protein diet for 24 hours prior to each condition of the experiment, and to fast from midnight prior. The ATD and Sham conditions started at 8:30 a.m. and were approximately 7 hours in duration. The amino acid drink was prepared minutes prior to ingestion by dissolving amino acids (Spectrum Chemicals & Laboratory Products, Gardena, CA, USA) in either 60 ml of chocolate syrup + 150 ml of tap water or 180 ml of orange juice, as preferred by the participant. The ATD drink was composed of the following large neutral

amino acids: L-alanine (5.5 g), glycine (3.2 g), L-histidine (3.2 g), L-isoleucine (8.0 g), L-leucine (13.5 g), L-lysine (11.0 g), L-phenylalanine (5.7 g), L-proline (12.2 g), L-serine (6.9 g), L-threonine (6.9 g), L-tyrosine (6.5 g), and L-valine (8.9 g). Amino acids with unpleasant taste and smell (L-arginine, 4.9 g; L-cysteine, 2.7 g; L-methionine, 3.0 g) were ingested separately, in a capsule form. A similar ATD composition has been used previously (Salomon et al., 2011; Von Ah et al., 2012). The ATD drink and capsule composition were identical to the Sham depletion drink/capsules with the exception of L-tryptophan (4.0 g), which was added to the Sham drink. Participants were provided with additional water to drink and a piece of fruit or fruit cups. In addition, some participants also consumed ginger ale and crackers over the duration of the afternoon.

Mood status and menopausal symptoms were assessed and a blood sample (20 ml) was drawn to measure plasma levels of phenylalanine, tyrosine, and other large neutral amino acids at 5 hours post drink ingestion. A depletion of ≥ 60% in tryptophan levels 5 hours after ATD drink ingestion indicated a successful depletion procedure (Delgado et al., 1999). During the first 5 hours post-ingestion, participants were invited to rest in a comfortable, quiet room with magazines or a TV, use their personal electronic devices to work or play games, and/or to stroll the hospital grounds.

Assessing Mood and Large Neutral Amino Acids

Upon arrival, prior to drink ingestion, participants were assessed for mood status (MADRS, POMS), and menopausal symptoms (GCS, and HFRDIS)

following which a blood sample (20 ml) was drawn. At 5 hours post-ingestion, Mood (POMS) and menopausal symptoms (GCS, HFRDIS) were rated, and blood samples collected, as this is the reported range of maximal tryptophan depletion (Hood et al., 2005). Mood raters were blind to the condition/drink ingested.

Blood Analysis

Within 30 min of collection, whole blood samples were centrifuged at 1,810 x g for 15 minutes at 4ºC, and the resulting plasma was aliquoted and stored at -80ºC until use. Whole blood samples were allowed to clot at room temperature for 30 – 60 minutes and then centrifuged at 1,810 x g for 10 minutes at 4ºC. The resulting serum was aliquoted and stored at -80ºC until use.

Calculation of Tryptophan Levels

Blood serum levels of tryptophan were ascertained via fluorometry. Tryptophan levels were calculated by ascertaining the ratio of free plasma levels of L-tryptophan to large neutral amino acids (L-isoleucine + L-leucine + L-tryptophan + L-valine). Tryptophan depletion levels were calculated by subtracting afternoon tryptophan levels from morning tryptophan levels, dividing by morning tryptophan levels and multiplying by 100.

Estrogen Analysis/Calculation

Analysis of estrogen levels in patient serum was completed using a competitive binding enzyme-linked immunosorbent assay following the manufacturer's instructions (11-ESTHU-E01, Alpco, Salem, NH, USA). A four-parameter logistic regression was used for curve fitting.

Emotional Conflict Task

The Emotional Conflict Task is comprised of 148 black and white happy or fearful faces with the word "HAPPY" or "FEAR" in upper case red letters superimposed just beneath the bridge of the nose, such that the word and the image were either congruent or incongruent (for more detailed information see Frey et al., 2010; Etkin and Schatzberg, 2011). Stimuli were presented for 1,000 milliseconds, with a jittered inter-stimulus interval of 3,000 to 5,000 milliseconds (mean inter-stimulus interval, 4,000 ms) during which a central fixation was displayed. Incongruent adaptation was defined as the contrast between measurements on the second of two consecutive incongruent trials (iI trials) and measurements on incongruent trials preceded by congruent trials (cI trials). There were no direct repetitions of the same face with varying word distracters nor any direct repetitions of exact face-word-distracter combinations, to avoid repetition or negative priming effects. Participants were instructed to respond as quickly and accurately as possible by pushing a button corresponding to the affect expressed in the image. RT and accuracy were dependent variables. For the RT analysis, error trials and post-error trials, and trials with RT more than 2 standard deviations below or above the mean for each trial type (cC, cI, iC or iI) were not included in the analysis. The total length of the task is approximately 13 minutes.

fMRI Acquisition

The scanning session commenced approximately 5.5 hours after drink ingestion and immediately following the second blood collection of the session, lasting

approximately 45 minutes. MRI was conducted in a MR 750 3T MRI whole body short bore scanner (General Electric Healthcare, Waukesha, WI, USA) with a 32-channel head coil (MR Instruments, Minneapolis, MN, USA). A 3-Plane localizer was run first, followed by ASSET calibration, an anatomical scan (9 minutes), a resting-state functional MRI (fMRI; resting state data not presented here), and the Emotional Conflict Task (13 minutes). Emotional Conflict Task Stimuli were presented with E-prime software (Schneider et al., 2002) version 2.0 onto a screen. Participants viewed the images on a mirror visor attached to the head coil. A 3-dimensional high-resolution T1-weighted fast spoiled gradient-echo anatomical image was acquired with images in the same session. The fMRI data for the Emotional Conflict Task was acquired in the axial plane with a top-down interleaved gradient echo echo-planar imaging sequence with repetition time=2000 ms, echo time=40ms, flip angle=90º, 4 mm slice thickness, with 29 slices, field of view=240 × 240 mm in a 64 × 64 matrix with full brain coverage.

Data files were converted from dicom to nifti using FreeSurfer's mri_convert (http://surfer.nmr.mgh.harvard.edu/). The first two volumes of functional data were discarded to remove volumes in which magnetization equilibrium had not been attained (Howseman et al., 1997).Functional images were analysed with SPM 12 (v6225) (2007). As data acquisition was interleaved, the remaining volumes were slice time corrected to account for a shifting time course (Sladky et al., 2011). Images were then realigned to account for slight head movement and physiological motion (respiration). Images were motion corrected

(Friston et al., 1996) and participants with motion > 4mm were flagged and removed from the analysis. Anatomical images were segmented into grey and white matter, CSF, and skull, and a deformation field was generated. Functional images for each participant were coregistered to their individual anatomical images, and then functional and anatomical images were spatially normalized into Montreal Neurological Institute (MNI) space (Friston et al., 1995) using the deformation field generated in the segmentation step. Finally, to filter out high frequency fluctuations images were spatially smoothed with a 6 mm full width half-maximum Gaussian kernel (Hopfinger et al., 2000).

At the subject level explanatory variables corresponding to *cI (incongruent trial preceded by congruent trial) trials, iI (incongruent trial preceded by incongruent trial) trials, iC (congruent trial preceded by incongruent trial) trials, cC (congruent trial preceded by congruent trial) trials, error trials* and *post-error trials*, were entered into the general linear model. Six movement parameters generated in the motion correction step were entered as explanatory variables of no interest, and a temporal high-pass filter of 128 seconds was applied to the data. At the group level, a random effects analysis was completed with paired t-tests with tryptophan depletion percentage entered as a covariate.

Whole-brain exploratory analyses for between-group comparisons of *all trials*, *congruent trials*, *incongruent trials*, *incongruent > congruent trials*, and *iI > cI trials* are presented with a threshold of $p < .001$ uncorrected, with a cluster-level 50-voxel cut off.

Statistical Analysis

Behavioural and demographic data were analyzed using SPSS 23 (IBM Corporation, 2015). Non-parametric statistics were calculated. All measures are reported as medians, unless otherwise noted.

Results

Twenty-eight participants completed the imaging protocol. Data for six participants was excluded due to movements exceeding 4 mm in translation or rotation during MRI testing, fMRI data was missing/incomplete for two participants, behavioural data was missing/incomplete for three participants, two participants consumed the drink for the second scan but were unable to complete the fMRI portion of the study, and one participant did not adhere to the diet, resulting in a final sample size of 14.

Demographics

Demographic information for the 14 remaining participants is listed in Table 1. Assessment with the MINI indicated that 36% of participants had no previous/current psychiatric diagnosis, 57% had past or recurrent Major Depressive episode(s), 7% were currently experiencing a Major Depressive episode, and 36% of participants had a diagnosis related to panic or anxiety disorders. Two participants had undergone hysterectomy.

Of the 14 participants, eight were not taking any additional medication, one patient was taking trandolapril, one participant was taking zopiclone, one participant was taking opioid medication (prescribed by her family doctor), one

participant was taking levothyroxine, and one participant was taking meloxicam and rabeprazole.

Tryptophan Depletion and Estradiol Measures

There was a significant difference in tryptophan depletion levels from Sham (median = 12.2%) to ATD (median = 96.1%) conditions, $z = -3.474$, $p < 0.0005$. The ATD mean 92.2% (SD = 7.8%) is in the high end of the range reported in previous studies (55% - 94%) (Richard et al., 2009). There were no significant differences in estrogen measures at either morning or afternoon between ATD and Sham conditions.

There were no significant correlations between morning or afternoon estrogen measurements and tryptophan depletion, in either Sham or ATD conditions.

Mood and Vasomotor Symptoms

Mood and vasomotor symptoms are reported in Table 2. Briefly, with the exception of the anger-hostility and vigor-activity subscales of the POMS, and sexual subscale of the GCS, all measures of mood and vasomotor symptoms from the POMS, GCS, MADRS and HFRDIS were significantly lower at Sham, compared to baseline. Compared to baseline, ATD measures for MADRS, HFRDIS, GCS and POMS were significantly lower, with the exception of the POMS subscales depression and vigor-activity, and the GCS subscales anxiety and sexual. Bonferroni corrected post-hoc tests indicated no differences between

Sham and ATD conditions in the MADRS, HFRDIS, or any of the POMS or GCS subscales.

Emotional Conflict Task Behavioural Statistics

Between condition differences

There were no differences between the ATD and Sham conditions for overall RT or overall accuracy. In addition, there were no significant differences between ATD and Sham in RT or accuracy on congruent trials, incongruent trials, iI minus cI trials (incongruent adaptation), or on incongruent minus congruent trials (emotional Stroop).

Within condition differences - Sham

There was a significant emotional Stroop effect in the Sham condition, with significantly faster RT on congruent (median = 786 ms) compared to incongruent (median = 728 ms) trials $z = -2.417$, $p = 0.016$. However, there was no significant difference in accuracy on emotional Stroop (see Table 3).

Differences in incongruent adaptation RT were not significant in the Sham condition. However, in the Sham condition, accuracy on iI trials was significantly higher (median = .92) than on cI trials (median = .89), $z = -2.370$, $p = 0.018$ (see Table 4).

Within condition differences - ATD

There was a significant emotional Stroop effect in the ATD condition, with significantly faster RT on congruent (median = 715 ms) compared to incongruent

(median = 769 ms) trials, $z = -3.107$, $p = 0.002$. However, there was no significant difference in accuracy on emotional Stroop (see Table 3).

RT on iI trials was significantly slower (median = 781 ms) compared to cI trials (median = 763 ms) in the ATD condition, $z = -2.103$, $p = 0.035$ (see Table 4), demonstrating the reverse of the pattern expected for incongruent adaptation. Differences in accuracy on incongruent adaptation were not significant in the ATD condition.

Neuroimaging

There were no significant differences between Sham and ATD for the comparison of All Faces, Congruent trials, or iI trials.

There was lower BOLD activation in ATD compared to Sham on incongruent adaptation in bilateral angular gyrus, right superior division of lateral occipital cortex, left caudate, and temporooccipital part of middle temporal gyrus (see Table 4 and Figure 1).

There was greater activation in ATD compared to Sham on incongruent trials in left thalamus and hippocampus (see Table 5). In addition, there was greater activation on cI trials in left hippocampus, thalamus, middle temporal gyrus, supramarginal gyrus, lateral occipital cortex, and cingulate gyrus. For the emotional Stroop, there was greater activation in ATD in left precuneus cortex, postcentral gyrus, angular gyrus, right cingulate gyrus, and bilateral superior parietal lobule, middle temporal gyrus, temporal occipital fusiform cortex, and lateral occipital cortex (see Figure 2).

Discussion

This study utilized an fMRI Emotional Conflict Task to examine the effect of ATD and ET on emotional information processing in perimenopausal women. While there were no differences between conditions behaviourally, neuroimaging results indicated an overall increase in BOLD activity in discrete brain regions in ATD, compared to the Sham condition.

Tryptophan Depletion and Estradiol Measures

ATD was successful with a mean depletion of 92.2%, which is within the range of depletion percentages reported in the literature (Richard et al., 2009).

Mood & Vasomotor Symptoms

Although there was a significant reduction in mood and vasomotor symptoms among symptomatic midlife women after initiating ET, these symptoms did not resurface significantly in the ATD condition. There were no differences between Sham and ATD conditions in measures of mood or vasomotor symptoms, indicating that temporary tryptophan depletion was insufficient to reverse the benefits of ET on mood and vasomotor symptoms.

Emotional Conflict Task Behavioural Statistics

Behaviourally, there were no differences between Sham and ATD conditions in RT or accuracy on the Emotional Conflict Task, similar to findings using a traditional colour-word Stroop task in a female HC group undergoing ATD (Evers et al., 2006).

Within both Sham and ATD conditions, there was a robust emotional Stroop effect in both the Sham and ATD conditions as measured by RT, with faster RT on congruent compared to incongruent trials, as has been previously reported in healthy comparison groups (Etkin et al., 2006; Frey et al., 2010; Wortinger et al., 2017) and in a sample of early peri-menopausal to late menopausal mid-life women not receiving HT (Frey et al., 2010). However, the expected emotional Stroop effect of higher accuracy on congruent compared to incongruent trials (Etkin et al., 2006; Gold et al., 2015; Wortinger et al., 2017) was not demonstrated in Sham or ATD. This is similar to findings in a sample of early peri-menopausal to late menopausal mid-life women not receiving HT, using the same Emotional Conflict Task (Frey et al., 2010). This suggests that failure to detect an emotional Stroop effect in accuracy may not necessarily be related to the influence of ET in this sample.

In the Sham condition, participants demonstrated incongruent adaptation in accuracy but not in RT. Similar results have been reported in a variety of emotional conflict tasks (Krug and Carter, 2010; Clayson and Larson, 2013; Chechko et al., 2014; Gold et al., 2015). Conversely, in the ATD condition, participants took significantly longer to respond on iI trials, compared to cI trials, which is the opposite of the expected pattern (Etkin et al., 2006; Chechko et al., 2009), with no concomitant advantage conferred in emotional information processing. Failure of the conflict introduced in the first incongruent presentation of an iI trial to enhance the behavioural response to the second incongruent trial

demonstrates a lack of incongruent adaptation, which is also reflected in the lack of difference in accuracy in identifying the emotional expression in either trial type. Interestingly, this same pattern of slower RT on iI compared to cI trials and no incongruent adaptation in accuracy has been previously demonstrated in a group of mid-life women not receiving HT under regular testing conditions (Frey et al., 2010).

Consider the possibility of two dissociable components to incongruent adaptation involving facilitation of task completion (RT) and competence in task execution (accuracy) (Gold et al., 2015). In this case, in the Sham condition, participants were able to demonstrate incongruent adaptation in task execution, without the concomitant facilitation in task completion. ATD did not enhance response execution and appears to have interfered with response facilitation, with a significant slowing of responses on iI compared to cI trials. These results may be contrasted to findings in which a group of mid-life women did not demonstrate incongruent adaptation in either task completion or execution, which suggests that ET may modulate this behavioural response in menopausal women (Frey et al., 2010).

Neuroimaging

There was lower BOLD activity in ATD compared to Sham for the incongruent adaptation comparison in angular gyrus, lateral occipital cortex, caudate, and middle temporal gyrus. The middle temporal gyrus is involved in emotion cognition (Iidaka et al., 2001), while the caudate is a component in a circuit

important for emotion regulation (Alexander et al., 1986). Reduced BOLD activity in these regions, together with the attenuation of incongruent adaptation execution in the ATD condition and a reversal of the expected facilitation of response in incongruent adaptation suggests that serotonin may influence emotional information processing of conflicting emotional information.

Greater BOLD activity in ATD compared to Sham on incongruent trials, cI trials, and emotional Stroop suggests that in ATD it may be necessary for additional neural regions to be recruited to compensate for a reduction in available serotonin to attain the same levels of behavioural responding as in the Sham condition.

Conclusions

In sum, ATD does not appear to affect mood, or vasomotor symptoms among women receiving treatment with ET. It is plausible to consider that the effects of ET on mood and thermoregulation are not primarily mediated by serotonergic and noradrenergic systems, respectively. Conversely, one could hypothesize that a high dose of transdermal ET was sufficient to secure a homeostatic state that prevents women from experiencing a rapid deterioration of mood while in ATD.

Temporarily lowering serotonin levels through ATD, allows us to examine effect of low serotonin on processing of emotional information without the confound presented by low mood (Beacher et al., 2011). While behavioural responding was largely unaffected in ATD compared to Sham, it was interesting to observe the attenuation of incongruent adaptation in ATD compared to Sham. It

is possible that temporary tryptophan depletion is insufficient to elicit significant observable changes in mood and vasomotor symptoms, and that greater changes in emotional information processing might emerge only after prolonged tryptophan depletion. Just as Parkinson's symptoms aren't observed until striatal dopamine loss reaches approximately 80% (Fearnley and Lees, 1991).

This is the first study to examine the effect of acute tryptophan depletion on emotional Stroop in a sample of midlife women receiving transdermal ET. A more detailed picture of the varied effects of ATD on mood, vasomotor symptoms, and emotional information processing may have emerged with the addition of a baseline Sham and ATD testing of participants prior to starting ET. Future studies may also include a neutral condition in the Emotional Conflict Task to observe how ATD may influence interpretation of a neutral or ambiguous facial expression of emotion.

Tables and Figures

Table 1. Participant demographic information

Variable	
Group *n*	14
Right/Left handed[X] *n* (%)	8/2 (57%/14%)
Age in years	51 ± 4.3
Age at Menarche in years	13.5 ± 1.2
Baseline MADRS	14 ± 7
Baseline HFRDIS	40 ± 32
STRAW Stages *n* (%)	
+1a (< 1 year since final menstrual period)	6 (43%)
+1b (> 1 year since final menstrual period)	5 (36%)
+1c (> 5 years since final menstrual period)	3 (21%)
Ethnicity *n* (%)	
Aboriginal	1 (7%)
Asian	1 (7%)
Black/Afro-Caribbean/African	1 (7%)
White/European	11 (79%)
Level of Education Attained *n* (%)	
Some High School	1 (7%)
Completed High School	1 (7%)
Some College/University	3 (21%)
Completed College/University/Graduate School	9 (64%)
Marital Status *n* (%)	
Other	1 (7%)
Separated/Divorced	4 (28%)
Married/Domestic Partnership	8 (57%)
Widowed	1 (7%)

Note. Unless otherwise indicated, data are reported as Mean ± Standard Deviation.
MADRS. Montgomery-Åsberg Depression Rating Scale.
HFRDIS. Hot Flash Related Daily Interference Scale
STRAW. Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.
[X]Data for four participants missing.

Table 2. Mood symptom assessment at baseline and post-drink ingestion in ATD and Sham conditions

Instrument	Variable	Baseline	Sham	ATD	Test[#]
MADRS†	Total Score	13.5	1.5**	1.0***	$\chi^2(2) = 20.32$, $p < 0.0005$
POMS	Tension-anxiety	9	4*	4.5*	$\chi^2(2) = 11.54$, $p = 0.003$
	Depression	9.5	0*	0	$\chi^2(2) = 11.53$, $p = 0.003$
	Anger-hostility	5.5	.5	0*	$\chi^2(2) = 10.09$, $p = 0.006$
	Vigor-activity	11	16	14	$\chi^2(2) = 2.46$, $p = 0.292$
	Fatigue	9	4.5**	4**	$\chi^2(2) = 16.13$, $p < 0.0005$
	Confusion-bewilderment	7.8	3*	3.5*	$\chi^2(2) = 13.04$, $p = 0.001$
GCS	Anxiety	6	2**	2.5	$\chi^2(2) = 10.11$, $p = 0.006$
	Depression	4.5	1***	1**	$\chi^2(2) = 20.32$, $p < 0.0005$
	Somatic	4	1.5*	2*	$\chi^2(2) = 10.92$, $p = 0.004$
	Vasomotor	2.5	.5*	1*	$\chi^2(2) = 13.56$, $p = 0.001$
	Sexual	1.5	.5	0	$\chi^2(2) = 5.20$, $p = 0.074$
HFRDIS[‡]	Total	42	1**	1.5**	$\chi^2(2) = 16.55$, $p < 0.0005$

MADRS – Montgomery-Åsberg Depression Rating Scale; POMS – Profile of Mood States; GCS – Greene Climacteric Scale; HFRDIS – Hot Flash Related Daily Interference Scale –

†MADRS was completed only prior to morning drink ingestion during Sham and ATD testing.

[‡]Participants were instructed to consider the ratings as applying 'in the past week'; Data missing for one participant at Baseline.

[#]Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, with Bonferroni corrected post-hoc comparisons indicate significant difference from baseline at: *p < 0.05, ** p < 0.01 *** p < 0.001

Table 3. Emotional Stroop effect in the Emotional Conflict Task, as measured by reaction time and accuracy, in Sham and ATD conditions

Condition	Incongruent Reaction Time	Congruent Reaction Time	Test[#]
Sham	787	728	z = -2.417, p = 0.016*
ATD	769	715	z = -3.107, p = 0.002*
	Incongruent Accuracy	Congruent Accuracy	
Sham	.91	.92	z = 1.538, p = 0.124
ATD	.91	.91	z = -0.471, p = 0.638

Note: Medians are reported

* significant at $p = 0.05$; [#] Related-Samples Wilcoxon Signed Rank Test

Table 4. Incongruent Adaptation in the Emotional Conflict Task, as measured by reaction time and accuracy in Sham and ATD conditions

Condition	iI Reaction Time	cI Reaction Time	Test[#]
Sham	771	790	z = 0.758, p = 0.433
ATD	781	763	z = -2.103, p = 0.035*
	iI Accuracy	cI Accuracy	
Sham	.92	.89	z = -2.370, p = 0.018*
ATD	.91	.89	z = -0.358, p = 0.720

Note: Medians are reported. iI (incongruent trial preceded by an incongruent trial), cI (incongruent trial preceded by a congruent trial).
* significant at $p = 0.05$; [#] Related-Samples Wilcoxon Signed Rank Test

Table 5. Comparison of Sham > ATD, in the Emotional Conflict Task, fMRI Results

Comparison/ Anatomical Region	BA	MNI Coordinates			t-value*	Cluster Size
		x	y	z		
iI minus cI trials						
Angular gyrus	39	42	-52	30	7.95	86
Caudate	48	-14	12	12	7.35	82
Lateral occipital cortex, superior division	7	20	-60	58	5.81	66
Lateral occipital cortex, superior division	7	32	-60	54	4.34	
Angular gyrus	39	-40	-60	34	5.66	65
Middle temporal gyrus, temporooccipital part	39	-54	-52	10	5.54	51
Middle temporal gyrus, temporooccipital part	39	-46	60	10	5.46	
Angular gyrus	39	-46	54	16	4.21	

Note: iI (incongruent trial preceded by an incongruent trial), cI (incongruent trial preceded by a congruent trial). BA = Brodmann Area.
*Results are uncorrected at $p < 0.001$, extent threshold, 50 voxels.

Table 6. Comparison of ATD > Sham, in the Emotional Conflict Task, fMRI Results

Comparison/ Anatomical Region	BA	MNI Coordinates			t-value*	Cluster Size
		x	y	z		
Incongruent trials						
Thalamus/Hippocampus	50	-18	-36	4	5.51	55
cI trials						
Thalamus	-	-6	-26	16	4.52	58
Thalamus	-	-16	-30	16	3.52	
Middle temporal gyrus, temporooccipital part	39	-52	-56	10	3.81	79
Supramarginal gyrus, posterior division	-	-46	-48	14	3.27	
Lateral occipital cortex, inferior division	39	-50	-64	12	3.19	
Hippocampus	-	-16	-38	4	3.72	88
Thalamus	-	-26	-32	0	3.64	
Cingulate gyrus, posterior division	30	-12	-44	8	3.31	
Incongruent minus Congruent trials						
Postcentral gyrus	-	-18	-46	46	8.08	74
Superior parietal lobule	7	-28	-50	44	5.97	
Precuneus cortex	7	-10	-46	48	4.16	
Precuneus cortex	-	-18	-56	38	8.01	81
Cerebral white matter	-	30	-18	32	7.66	59
Cerebral white matter	-	40	-24	32	7.11	
Superior parietal lobule	-	22	-54	42	7.55	745
Precuneus cortex	31	-2	-48	44	6.98	

Table 6. (Continued)

Comparison/ Anatomical Region	BA	MNI Coordinates			t-value*	Cluster Size
		x	y	z		
Incongruent minus Congruent trials						
Cingulate gyrus, posterior division	23	14	-42	34	6.57	
Precuneus cortex	-	-28	-58	2	6.95	110
Temporal occipital fusiform cortex	-	-36	-46	-8	6.86	
Temporal occipital fusiform cortex	-	38	-52	-6	6.85	69
Middle temporal gyrus, temporooccipital part		42	-48	6	5.22	
Angular gyrus	21	-44	-52	12	6.48	79
Middle temporal gyrus, posterior division		-44	-42	2	5.44	
Lateral occipital cortex, superior division	39	42	-64	20	6.04	52
Lateral occipital cortex, superior division	19	40	-74	22	5.30	
Hippocampus	-	-18	-42	6	5.35	65
Precuneus cortex	23	-14	-50	12	5.26	
Precuneus cortex	30	-20	-50	6	4.85	
Lateral occipital cortex, inferior division	37	-54	-64	-4	5.18	94
Lateral occipital cortex, inferior division	19	-44	-70	-2	4.84	

Note: cI (incongruent trial preceded by a congruent trial). BA = Brodmann Area.

*Results are uncorrected at $p < 0.001$, extent threshold 50 voxels.

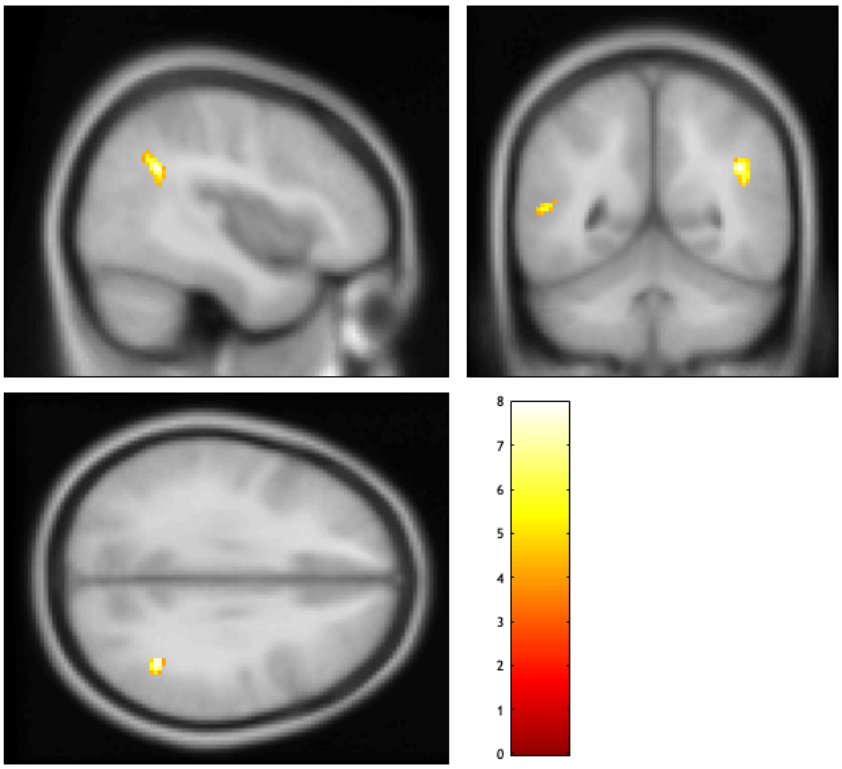

Figure 1. Incongruent Adaptation: Sham > ATD

As described in Table 5, activation in right angular gyrus (t = 7.95, uncorrected) is greater in Sham compared to ATD condition. MNI coordinates: (x = 42, y = 52, z = 30). Statistical maps are superimposed on MNI 152 T1 1 mm standard brain averaged group image and presented in neurological convention. Results are uncorrected at $p < 0.001$, extent threshold 50 voxels.

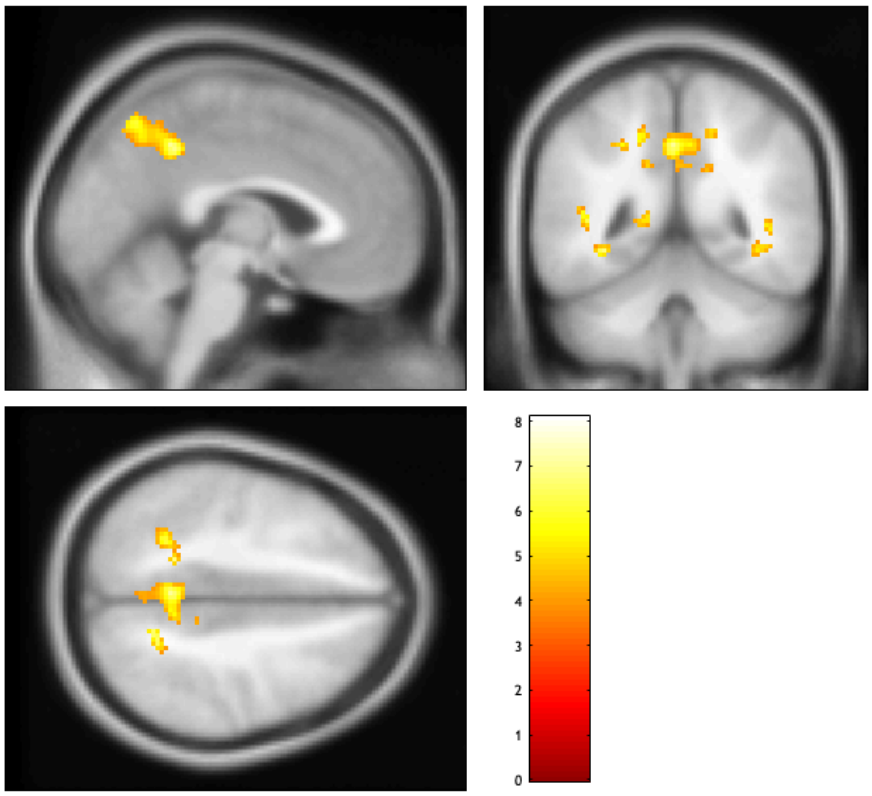

Figure 2. Emotional Stroop: ATD > Sham

As described in Table 6, activation in left precuneus extending to right superior parietal lobule and posterior cingulate cortex (Brodmann areas R 23/L31), (t = 7.55, uncorrected) is greater in ATD compared to Sham conditions. MNI coordinates: (x = -2, y = -48, z = 44). Statistical maps are superimposed on MNI 152 T1 1 mm standard brain averaged group image and presented in neurological convention. Results are uncorrected at $p < 0.001$, extent threshold 50 voxels.

References

(2007). *Statistical parametric mapping: the analysis of functional brain images*. Amsterdam: Elsevier.

Alexander, G.E., DeLong, M.R., and Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9**,** 357-381. doi: 10.1146/annurev.ne.09.030186.002041.

Baranyi, A., Amouzadeh-Ghadikolai, O., von Lewinski, D., Breitenecker, R.J., Rothenhausler, H.B., Robier, C., et al. (2017). Revisiting the tryptophan-serotonin deficiency and the inflammatory hypotheses of Major Depression in a biopsychosocial approach. *PeerJ* 5**,** e3968. doi: 10.7717/peerj.3968.

Beacher, F.D., Gray, M.A., Minati, L., Whale, R., Harrison, N.A., and Critchley, H.D. (2011). Acute tryptophan depletion attenuates conscious appraisal of social emotional signals in healthy female volunteers. *Psychopharmacology (Berl)* 213(2-3)**,** 603-613. doi: 10.1007/s00213-010-1897-5.

Bethea, C.L., Lu, N.Z., Gundlah, C., and Streicher, J.M. (2002). Diverse actions of ovarian steroids in the serotonin neural system. *Front Neuroendocrinol* 23(1)**,** 41-100. doi: 10.1006/frne.2001.0225.

Booij, L., Van der Does, W., Benkelfat, C., Bremner, J.D., Cowen, P.J., Fava, M., et al. (2002). Predictors of mood response to acute tryptophan depletion. A reanalysis. *Neuropsychopharmacology* 27(5)**,** 852-861. doi: 10.1016/S0893-133X(02)00361-5.

Bromberger, J.T., and Epperson, C.N. (2018). Depression during and after the perimenopause: Impact of hormones, genetics, and environmental determinants of disease. *Obstet Gynecol Clin North Am* 45(4)**,** 663-678. doi: 10.1016/j.ogc.2018.07.007.

Bromberger, J.T., Kravitz, H.M., Chang, Y.F., Cyranowski, J.M., Brown, C., and Matthews, K.A. (2011). Major Depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med* 41(09)**,** 1879-1888. doi: 10.1017/s003329171100016x.

Bromberger, J.T., Schott, L., Kravitz, H.M., and Joffe, H. (2015). Risk factors for major depression during midlife among a community sample of women

with and without prior Major Depression: are they the same or different? *Psychol Med* 45(8), 1653-1664. doi: 10.1017/S0033291714002773.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada (December 2014). "Tri-council policy statement: Ethical conduct for research involving humans".).

Carpenter, J.S. (2001). The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage* 22(6), 979-989. doi: 10.1016/S0885-3924(01)00353-0.

Chechko, N., Kellermann, T., Schneider, F., and Habel, U. (2014). Conflict adaptation in emotional task underlies the amplification of target. *Emotion* 14(2), 321-330. doi: 10.1037/a0035208.

Chechko, N., Wehrle, R., Erhardt, A., Holsboer, F., Czisch, M., and Samann, P.G. (2009). Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder. *PLoS One* 4(5), e5537. doi: 10.1371/journal.pone.0005537.

Clayson, P.E., and Larson, M.J. (2013). Adaptation to emotional conflict: evidence from a novel face emotion paradigm. *PLoS One* 8(9), e75776. doi: 10.1371/journal.pone.0075776.

Cohen, L.S., Soares, C.N., Vitonis, A.F., Otto, M.W., and Harlow, B.L. (2006). Risk for new onset depression during the menopausal transition. *Arch Gen Psychiatry* 63, 385-390. doi: 10.1001/archpsyc.63.4.385.

Delgado, P.L., Miller, H.L., Salomon, R.M., Licinio, J., Krystal, J.H., Moreno, F.A., et al. (1999). Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. *Biol Psychiatry* 46(2), 212-220. doi: 10.1002/14651858.CD000402.pub4.

Ellenbogen, M.A., Young, S.N., Dean, P., Palmour, R.M., and Benkelfat, C. (1996). Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. *Neuropsychopharmacology* 15(5), 465 - 474. doi: 10.1016/S0893-133X(96)00056-5.

Epperson, C.N., Amin, Z., Naftolin, F., Cappiello, A., Czarkowski, K.A., Stiklus, S., et al. (2007). The resistance to depressive relapse in menopausal

women undergoing tryptophan depletion. *J Psychopharmacol* 21(4)**,** 414-420. doi: 10.1177/0269881106067330.

Epperson, C.N., Amin, Z., Ruparel, K., Gur, R., and Loughead, J. (2012). Interactive effects of estrogen and serotonin on brain activation during working memory and affective processing in menopausal women. *Psychoneuroendocrinology* 37(3)**,** 372-382. doi: 10.1016/j.psyneuen.2011.07.007.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51(6)**,** 871-882. doi: 10.1016/j.neuron.2006.07.029.

Etkin, A., and Schatzberg, A.F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in Generalized Anxiety and Major Depressive Disorders. *Am J Psychiatry* 168(9)**,** 968-978. doi: 10.1176/appi.ajp.2011.10091290.

Evers, E.A., van der Veen, F.M., Jolles, J., Deutz, N.E., and Schmitt, J.A. (2006). Acute tryptophan depletion improves performance and modulates the BOLD response during a Stroop task in healthy females. *Neuroimage* 32(1)**,** 248-255. doi: 10.1016/j.neuroimage.2006.03.026.

Fearnley, J.M., and Lees, A.J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 114 (Pt 5)**,** 2283-2301. doi: 10.1093/brain/114.5.2283.

Fernstrom, J.D., Langham, K.A., Marcelino, L.M., Irvine, Z.L., Fernstrom, M.H., and Kaye, W.H. (2013). The ingestion of different dietary proteins by humans induces large changes in the plasma tryptophan ratio, a predictor of brain tryptophan uptake and serotonin synthesis. *Clin Nutr* 32(6)**,** 1073-1076. doi: 10.1016/j.clnu.2012.11.027.

Freedman, R.R. (2010). Treatment of menopausal hot flashes with 5-hydroxytryptophan. *Maturitas* 65(4)**,** 383-385. doi: 10.1016/j.maturitas.2009.11.025.

Freeman, E.W., Sammel, M.D., Boorman, D.W., and Zhang, R. (2014). Longitudinal pattern of depressive symptoms around natural menopause. *JAMA Psychiatry* 71(1)**,** 36-43. doi: 10.1001/jamapsychiatry.2013.2819.

Freeman, E.W., Sammel, M.D., Liu, L., Gracia, C.R., Nelson, D.B., and Hollander, L. (2004). Hormones and menopausal status as predictors of

depression in women in transition to menopause. *Arch Gen Psychiatry* 61**,** 62-70. doi: 10.1001/archpsyc.61.1.62.

Frey, B.N., Hall, G.B., Attard, S., Yucel, K., Skelin, I., Steiner, M., et al. (2010). Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point? *Menopause* 17(4)**,** 840-845. doi: 10.1097/gme.0b013e3181df840f.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., and Frackowiak, R.S.J. (1995). Spatial registration and normalization of images. *Hum Brain Mapp* 2**,** 165-189. doi: 10.1002/hbm.460030303

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., and Turner, R. (1996). Movement-related effects in fMRI time-series. *Magn Reson Med* 35(3)**,** 346-355. doi: 10.1002/mrm.1910350312.

Fusar-Poli, P., Allen, P., McGuire, P., Placentino, A., Cortesi, M., and Perez, J. (2006). Neuroimaging and electrophysiological studies of the effects of acute tryptophan depletion: a systematic review of the literature. *Psychopharmacology (Berl)* 188(2)**,** 131-143. doi: 10.1007/s00213-006-0493-1.

Georgakis, M.K., Thomopoulos, T.P., Diamantaras, A.A., Kalogirou, E.I., Skalkidou, A., Daskalopoulou, S.S., et al. (2016). Association of age at menopause and duration of reproductive period with depression after menopause: a systematic review and meta-analysis. *JAMA Psychiatry* 73(2)**,** 139-149. doi: 10.1001/jamapsychiatry.2015.2653.

Gold, A.L., Jarcho, J.M., Rosen, D.K., Pine, D.S., and Ernst, M. (2015). Emotional and nonemotional conflict processing in pediatric and adult anxiety disorders. *J Child Adolesc Psychopharmacol* 25(10)**,** 754-763. doi: 10.1089/cap.2015.0066.

Gordon, J.L., and Girdler, S.S. (2014). Hormone replacement therapy in the treatment of perimenopausal depression. *Curr Psychiatry Rep* 16(12)**,** 517. doi: 10.1007/s11920-014-0517-1.

Gordon, J.L., Rubinow, D.R., Eisenlohr-Moul, T.A., Xia, K., Schmidt, P.J., and Girdler, S.S. (2018). Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry* 75(2)**,** 149-157. doi: 10.1001/jamapsychiatry.2017.3998.

Greene, J.G. (1998). Constructing a standard climacteric scale. *Maturitas* 29(1), 25-31. doi: 10.1016/SO378-5122(98)00025-5.

Hantsoo, L., and Epperson, C.N. (2015). Premenstrual Dysphoric Disorder: epidemiology and treatment. *Curr Psychiatry Rep* 17(11), 87. doi: 10.1007/s11920-015-0628-3.

Harlow, S.D., Gass, M., Hall, J.E., Lobo, R., Maki, P., Rebar, R.W., et al. (2012). Executive summary of the Stages of Reproductive Aging Workshop + 10. *Menopause* 19(4), 387-395. doi: 10.1097/gme.0b013e31824d8f40.

Henderson, J.A., and Bethea, C.L. (2008). Differential effects of ovarian steroids and raloxifene on serotonin 1A and 2C receptor protein expression in macaques. *Endocrine* 33(3), 285-293. doi: 10.1007/s12020-008-9087-5.

Hood, S.D., Bell, C.J., and Nutt, D.J. (2005). Acute tryptophan depletion. Part I: rationale and methodology. *Aust N Z J Psychiatry* 39(7), 558-564. doi: 10.1080/j.1440-1614.2005.01627.x.

Hopfinger, J.B., Buchel, C., Holmes, A.P., and Friston, K.J. (2000). A study of analysis parameters that influence the sensitivity of event-related fMRI analyses. *Neuroimage* 11(4), 326-333. doi: 10.1006/nimg.2000.0549.

Howseman, A.M., Josephs, O., Rees, G., and Friston, K.J. (1997). "Special issues in functional magnetic resonance imaging," in *Human Brain Function*. 1st ed: Academic Press), 1-20.

IBM Corporation (2015). "IBM SPSS Statistics for Macintosh, Version 23.0". 23.0 ed. (Armonk, NY, USA: IBM Corporation).

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., et al. (2001). Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *J Cogn Neurosci* 13(8), 1035-1047. doi: 10.1162/089892901753294338.

Jovanovic, H., Lundberg, J., Karlsson, P., Cerin, A., Saijo, T., Varrone, A., et al. (2008). Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. *Neuroimage* 39(3), 1408-1419. doi: 10.1016/j.neuroimage.2007.10.016.

Krug, M.K., and Carter, C.S. (2010). Adding fear to conflict: a general purpose cognitive control network is modulated by trait anxiety. *Cogn Affect Behav Neurosci* 10(3), 357-371. doi: 10.3758/CABN.10.3.357.

Lokuge, S., Frey, B.N., Foster, J.A., Soares, C.N., and Steiner, M. (2011). Depression in women: windows of vulnerability and new insights into the link between estrogen and serotonin. *J Clin Psychiatry* 72(11)**,** e1563-1569. doi: 10.4088/JCP.11com07089.

Maki, P.M., Kornstein, S.G., Joffe, H., Bromberger, J.T., Freeman, E.W., Athappilly, G., et al. (2018). Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause* 25(10)**,** 1069-1085. doi: 10.1097/GME.0000000000001174.

Marcus, S.M. (2009). Depression during pregnancy: rates, risks and consequences--Motherisk Update 2008. *Can J Clin Pharmacol* 16(1)**,** e15-22.

Marsh, W.K., Bromberger, J.T., Crawford, S.L., Leung, K., Kravitz, H.M., Randolph, J.F., et al. (2017). Lifelong estradiol exposure and risk of depressive symptoms during the transition to menopause and postmenopause. *Menopause* 24(12)**,** 1351-1359. doi: 10.1097/GME.0000000000000929.

Menkes, D.B., Coates, D.C., and Fawcett, J.P. (1994). Acute tryptophan depletion aggravates premenstrual sydrome. *J Affect Disord* 32**,** 37-44. doi: 10.1016/0165-0327(94)90059-0.

Montgomery, S.A., and Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *Brit J Psychiat* 134**,** 382-389. doi: 10.1192/bjp.134.4.382.

Morrison, M.F., Kallan, M.J., Ten Have, T., Katz, I., Tweedy, K., and Battistini, M. (2004). Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 55(4)**,** 406-412. doi: 10.1016/j.biopsych.2003.08.011.

Moses-Kolko, E. (2003). Widespread increases of cortical serotonin type 2A receptor availability after hormone therapy in euthymic postmenopausal women. *Fertility and Sterility* 80(3)**,** 554-559. doi: 10.1016/s0015-0282(03)00973-7.

Okazawa, H., Leyton, M., Benkelfat, C., Mzengeza, S., and Diksic, M. (2000). Statistical mapping analysis of serotonin synthesis images generated in healthy volunteers using positron-emission tomography and α-[^{11}C]methyl-L-tryptophan. *J Psychiatry Neurosci* 25(4)**,** 359-370.

Pollock, V., Cho, D.W., Reker, D., and Volavka, J. (1979). Profile of Mood States: the factors and their physiological correlates. *J Nerv Ment Dis* 167(10)**,** 612-614. doi: 10.1097/00005053-197910000-00004.

Richard, D.M., Dawes, M.A., Mathias, C.W., Acheson, A., Hill-Kapturczak, N., and Dougherty, D.M. (2009). L-Tryptophan: basic metabolic functions, behavioral research and therapeutic indications. *Int J Tryptophan Res* 2**,** 45-60. doi: 10.4137/IJTR.S2129.

Salomon, R.M., Cowan, R.L., Rogers, B.P., Dietrich, M.S., Bauernfeind, A.L., Kessler, R.M., et al. (2011). Time series fMRI measures detect changes in pontine raphe following acute tryptophan depletion. *Psychiatry Res* 191(2)**,** 112-121. doi: 10.1016/j.pscychresns.2010.10.007.

Santoro, N. (2016). Perimenopause: from research to practice. *J Womens Health (Larchmt)* 25(4)**,** 332-339. doi: 10.1089/jwh.2015.5556.

Schaechter, J.D., and Wurtman, R.J. (1990). Serotonin release varies with brain tryptophan levels. *Brain Res* 5(1-2)**,** 203-210. doi: 10.1016/0006-8993(90)91761-5.

Schmidt, P.J., Nieman, L., Danaceau, M.A., Tobin, M.B., Roca, C.A., Murphy, J.H., et al. (2000). Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 183(2)**,** 414-420. doi: 10.1067/mob.2000.106004.

Schneider, W., Eschman, A., and Zuccolotto, A. (2002). *E-Prime User's Guide*. Pittsburgh: Psychology Software Tools, Inc.

Shanmugan, S., Loughead, J., Cao, W., Sammel, M.D., Satterthwaite, T.D., Ruparel, K., et al. (2017). Impact of tryptophan depletion on executive system function during menopause is moderated by childhood adversity. *Neuropsychopharmacology* 42(12)**,** 2398-2406. doi: 10.1038/npp.2017.64.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20**,** 22-57. doi: 10.1016/S0924-9338(97)83296-8.

Sladky, R., Friston, K.J., Trostl, J., Cunnington, R., Moser, E., and Windischberger, C. (2011). Slice-timing effects and their correction in functional MRI. *Neuroimage* 58(2)**,** 588-594. doi: 10.1016/j.neuroimage.2011.06.078.

Smith, L.J., Henderson, J.A., Abell, C.W., and Bethea, C.L. (2004). Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of Macaques. *Neuropsychopharmacology* 29(11)**,** 2035-2045. doi: 10.1038/sj.npp.1300510.

Soares, C.N., Almeida, O.P., Joffe, H., and Cohen, L.S. (2001). Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 58**,** 529-534. doi: 10.1001/archpsyc.58.6.529.

Soares, C.N., and Zitek, B. (2008). Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci* 33(4)**,** 331-343.

Soules, M.R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., et al. (2001). Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric* 4(4)**,** 267-272. doi: Doi 10.1089/152460901753285732.

Steiner, M. (2003). Hormones and mood: from menarche to menopause and beyond. *J Affect Disord* 74(1)**,** 67-83. doi: 10.1016/s0165-0327(02)00432-9.

Stute, P., Neulen, J., and Wildt, L. (2016). The impact of micronized progesterone on the endometrium: a systematic review. *Climacteric* 19(4)**,** 316-328. doi: 10.1080/13697137.2016.1187123.

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel (2017). The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 24(7)**,** 728-753. doi: 10.1097/gme.0000000000000921.

Von Ah, D., Skaar, T., Unverzagt, F., Yu, M., Wu, J., Schneider, B., et al. (2012). Evaluating the role of serotonin on neuropsychological function after breast cancer using acute tryptophan depletion. *Biol Res Nurs* 14(1)**,** 5-15. doi: 10.1177/1099800410393273.

World Health Organization (2008). *The Global Burden of Disease 2004 Update* Geneva: World Health Organization.

World Health Organization (2017). *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization.

Wortinger, L.A., Endestad, T., Melinder, A.M., Oie, M.G., Sulheim, D., Fagermoen, E., et al. (2017). Emotional conflict processing in adolescent chronic fatigue syndrome: a pilot study using functional magnetic resonance imaging. *J Clin Exp Neuropsychol* 39(4)**,** 355-368. doi: 10.1080/13803395.2016.1230180.

Chapter 4

Reduced Accuracy Accompanied by Reduced Neural Activity During the Performance of an Emotional Conflict Task by Unmedicated Patients with Major Depression: A CAN-BIND Report

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Abstract

Background: Individuals with depression exhibit attenuated reactivity to both positive and negative emotional stimuli. This study examined differences in behavioural performance and in blood-oxygen level dependent (BOLD) neural activation patterns between unmedicated individuals with major depressive disorder (MDD) and healthy comparison participants (HC) on an emotional conflict task.

Methods: We studied 48 MDD and 30 HC who performed an emotional conflict task in a functional magnetic resonance imaging (fMRI) scanner.

Results: On the emotional conflict task, MDD and HC demonstrated a robust emotional Stroop effect in reaction time and accuracy. Overall accuracy was lower in MDD compared to HC with no significant reaction time differences. The fMRI data indicated lower BOLD activation in MDD compared to HC on comparisons of all trials, congruent, incongruent, and incongruent > congruent trials in regions including right inferior temporal gyrus, lateral occipital cortex, and occipital fusiform gyrus. Behavioural and neuroimaging data indicated no group differences in fearful versus happy face processing.

Limitations: Inclusion of a neutral condition may have provided a valuable contrast to how MDD and HC process stimuli without emotional valence compared to stimuli with a strong emotional valence.

Conclusions: MDD and HC demonstrated a robust emotional Stroop effect. Compared to HC, MDD demonstrated an overall reduced accuracy on the

emotional conflict task and reduced BOLD activity in regions important for face perception and emotion information processing, with no differences in responding to fearful versus happy faces. These findings provide support for the theory of emotion context insensitivity in individuals with depression.

Key Words: major depressive disorder, depression, emotion recognition, Stroop, emotional Stroop, emotional conflict task, fMRI.

Introduction

Individuals with depression exhibit attenuated reactivity to both positive and negative emotional stimuli (Rottenberg et al., 2005), with a tendency to express negative attentional biases (Peckham et al., 2010). Such a bias can translate into negative consequences in social interactions and affect decision-making with further consequent social outcomes (Scheele et al., 2013). The human face is an important source of dynamic emotional information in human interpersonal interactions. Darwin posited that fearful facial expressions evolved to convey information about dangerous situations, so that others could prepare for or prevent perilous circumstances (Darwin, 1872). There is evidence that individuals with major depressive disorder (MDD) show enhanced fear recognition (e.g., Bhagwagar et al., 2004), perhaps reflecting an overall negative bias when interpreting emotional stimuli. This tendency may also interact with a reciprocal bias involving decreased attention to positive emotional stimuli (Bourke et al., 2010; Duque & Vazquez, 2015), culminating in an overall reduction in emotional reactivity (Bylsma et al., 2008).

In a variation of the classical Stroop, which uses congruent and incongruent colour word labels (i.e., the word red displayed with red or blue letters) (Stroop, 1935), the Emotional Conflict Task (Etkin et al., 2006) uses both task-relevant and task-irrelevant information, which is emotionally valenced. The task comprises a series of happy or fearful facial expressions, on which an emotion word label that is either congruent or incongruent with the face emotion

is superimposed. The task measures the cognitive cost of suppressing task-irrelevant valenced stimulus features (the printed name of an emotion) to attend to task-relevant emotional information (the affect of a specific facial expression). The emotional Stroop effect is identified by increased reaction time (RT) on incongruent, compared to congruent trials (Hill & Knowles, 1991) and has been demonstrated in both healthy comparison participants (HC) (Chechko et al., 2009; Cheng et al., 2015; Etkin et al., 2006; Etkin & Schatzberg, 2011; Fournier et al., 2017; Wortinger et al., 2017) and in MDD (Etkin & Schatzberg, 2011; Fournier et al., 2017). An emotional Stroop effect in accuracy has also been reported on incongruent compared to congruent trials (Etkin et al., 2006; Favre et al., 2015; Fournier et al., 2017; Rey et al., 2014; Torres-Quesada et al., 2014). Comparing HC and unmedicated MDD, differences have not been observed in behavioural measures of accuracy and RT on a functional magnetic resonance imaging (fMRI) Emotional Conflict Task (Etkin et al., 2006; Fournier et al., 2017). Furthermore, one of the above studies failed to identify significant group differences between HC and MDD in blood oxygen-level dependent (BOLD) neural activity for incongruent versus congruent trials (Fournier et al., 2017).

In the Emotional Conflict Task, participant responses to one trial can be affected by the type of trial immediately preceding it. For example, in HC when an incongruent trial was preceded by a congruent trial (cI trial), the RT on the incongruent trial was slower (Chechko et al., 2009; Etkin et al., 2006; Etkin & Schatzberg, 2011), compared to an incongruent trial immediately preceded by an

incongruent trial (iI trial). Similar results have been shown in patients with MDD with slower RT on cI compared to iI trials (Etkin & Schatzberg, 2011). Incongruent trials generate a conflict flag that recruits cognitive resources to suppress task irrelevant stimuli (reading the name of the emotion). In the instance of an iI trial, a recognition of similar cognitive demands as the preceding incongruent trial results in a type of *incongruent adaptation* that is expressed in decreased RT to the second consecutive incongruent trial (Etkin et al., 2006; Sheth et al., 2012).

Healthy adults performing the Emotional Conflict Task show increased activity in rostral anterior cingulate cortex (Etkin et al., 2006) and ventral cingulate cortex (Etkin & Schatzberg, 2011), as well as reduced activity in the amygdala (Etkin et al., 2006; Etkin & Schatzberg, 2011) on iI compared to cI trials. By contrast, an unmedicated MDD group demonstrated decreased activity in ventral cingulate, and no changes in amygdala activation, compared to HC (Etkin & Schatzberg, 2011).

The objective of the present study was to examine differences in performance and brain activation patterns between unmedicated individuals with MDD and HC participants on an emotional conflict task. This study was conducted within the Canadian Biomarker Integration Network in Depression (CAN-BIND-1). A detailed description of the trial design has been published (Kennedy et al., 2019; Lam et al., 2016; MacQueen et al., 2019). We expected to find a robust emotional Stroop effect in both HC and MDD reflected in RT (Etkin

& Schatzberg, 2011; Fournier et al., 2017) and accuracy (Fournier et al., 2017). Between groups, we did not expect to see a significant difference in overall RT, or adaptation to iI trials (Etkin & Schatzberg, 2011). Accuracy has been reported lower in MDD compared to HC (Dalili et al., 2015; Rubinow & Post, 1992), while other studies have not found a difference (Etkin et al., 2006; Fournier et al., 2017). At the brain activity level, we expected to see greater BOLD activation in MDD in lateral prefrontal regions, to achieve similar levels of performance (Etkin & Schatzberg, 2011). Relative to HC, we expected to see less activity in anterior cingulate cortex in MDD on fear > happy trials, as negative expressions of affect are more similar to the emotional milieu participants with MDD experience (Davidson et al., 2003).

Materials and Methods

Participants

In the CAN-BIND-1 study, 86 MDD and 59 HC completed the Emotional Conflict Task. Institutional ethics boards at each site approved the study. Individuals with MDD were included if they met the following criteria: age between 18 and 60 years, Diagnostic and Statistical Manual IV-TR (American Psychiatric Association, 1994) criteria for a major depressive disorder as evaluated with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), the duration of the major depressive episode (MDE) was three months or longer, patients were free of psychotropic medication for at least five medication half-lives before baseline testing, scored 24 or greater on the

Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), and had adequate English language fluency to complete questionnaires and interviews. Exclusion criteria for MDD participants included: accompanying psychosis in current MDE, failure of four or more adequate pharmacological interventions, previous intolerance or non-response to escitalopram or aripiprazole, having initiated psychological treatment in the past three months with the intention of maintaining treatment, bipolar diagnosis, other primary psychiatric diagnoses, significant personality disorder that would preclude participant from completing the protocol (as judged by a clinician), or high suicide risk. Exclusion criteria for both HC and MDD included substance abuse/dependence in past six months, significant head trauma/neurological disorders or other unstable medical conditions, breastfeeding or pregnancy, or inability to participate in MRI portion of study. All participants provided written informed consent and were compensated for study participation.

Participants completed cognitive and fMRI measures at baseline, 2 weeks, and 8 weeks after starting treatment with escitalopram 10-20 mg/day. Only participants who completed all three time points were considered for inclusion in the study. Due to the volume of information generated by the current study, this paper focuses on within and between group comparisons at baseline only. Longitudinal within and between group comparisons will be published separately.

Study Procedure

Depression severity was assessed with the MADRS. Demographic, diagnostic, and psychiatric episode data were collected through interviews, and standardized self-report questionnaires (Kennedy et al., 2019; Lam et al., 2016; MacQueen et al., 2019).

The Emotional Conflict Task was used for fMRI data acquisition with a previously published trial sequence and parameters (Frey et al., 2010). The task comprises 148 black and white images (Ekman & Friesen, 1976) of fearful or happy faces, cropped to expose only the face. Each image was presented with the word "HAPPY" or "FEAR" in bold red uppercase lettering, overlaid on the image just below the bridge of the nose. Equal numbers of congruent (face affect and word label match) and incongruent (face affect and word do not match) presentations were counterbalanced and presented in two individual runs. Each run presented 74 stimuli and lasted 6 minutes and 35 seconds. Prior to the experiment, participants briefly practiced the task outside of the scanner to ensure instruction comprehension. Images were presented to participants in an MRI scanner using E-Prime version 2 (Schneider et al., 2002). Images were presented for 1 second. Participants were instructed to ignore the word printed on the face and identify the emotional affect observed in the face as accurately and quickly as possible, using a button box. Inter-trial intervals were jittered and varied between 3 and 5 seconds, during which participants were presented with a fixation cross. RT and accuracy were evaluated. Emotional Stroop effect refers to the longer RT

and decreased accuracy that occur when participants respond to incongruent trials, as compared to congruent trials. Incongruent adaptation ensues when performance, as measured by RT, improves on an iI trial, as compared to performance on a cI trial. Trials analyzed were: congruent, incongruent, happy, fearful, cC (congruent preceded by congruent trial), cI (incongruent preceded by congruent trial), iC (congruent preceded by incongruent trial), iI (incongruent preceded by incongruent trial).

For RT analysis, error trials, post-error trials (the trial following an error trial), and trials with an RT > 2 standard deviations above or below the trial type mean, were not included. The commission error threshold was set at 25% per run, and the threshold of total allowable errors (combined omission and commission errors) was set at 30% per run. For accuracy calculations, trials with an RT > 2 standard deviations from the trial type mean and post-error trials were included. Accuracy was calculated with the formula:

$$\%\ correct\ \text{trial type} = \frac{1 - (\text{trial type errors})}{(\text{number of events for trial type})}$$

Error trials were excluded in neuroimaging analyses of incongruent, congruent, happy, fearful, cI and iI trials and post-error trials were excluded from cI and iI trial analyses. For the neuroimaging analysis of *all trials*, all trials were included, regardless of RT or accuracy.

Participants also completed the computerized neurocognitive test battery CNS-Vital Signs (CNS-VS; Gualtieri & Johnson, 2006). Standardized domain scores (adjusted for age and sex) for RT, cognitive flexibility, executive functioning, and simple Stroop RT were included in our analysis.

Functional MRI Data Acquisition

Images were acquired on five 3 T whole body MRI scanners (one Tim Trio from Siemens, Germany; one Intera Achieva from Philips, Netherlands; one Signa HDxt and two Discovery MR 750 from GE Healthcare, USA), using multi-channel receive head coils. Whole head fMRI images were acquired with 4.0 mm isotropic voxels using a $T2^*$-weighted single-shot echo-planar gradient echo imaging sequence: FOV=256×256 mm; matrix=64×64; 36–40 4 mm oblique slices with no gap; TR=2000 ms, TE = 30 ms^2, flip angle=75º; parallel imaging R=2. Excluding discarded volumes, 376 volumes were collected per session, across 12.5 minutes scan time. Any deviations from the stated acquisition parameters at individual sites are listed in Table S2.

Preprocessing of fMRI data was performed using the OPPNI preprocessing pipeline v07.3.1_06JUL2017 (Churchill et al., 2015; Strother, 2006). Briefly, principal component analysis (PCA) was applied to the 4D fMRI dataset, to identify the volume with the smallest Euclidean distance from the median coordinates in PCA space which was considered as the volume with the least head displacement. This brain volume was used as a reference for the Motion Correction (MOTCOR) step. Next, rigid-body MOTCOR was applied

using AFNI's (Cox, 1996) 3dvolreg algorithm, transforming each 4D image to match the volume with minimum estimated displacement. Outlier brain volumes were censored by removal and replacement with interpolated values from adjacent volumes (Campbell et al., 2013; Churchill et al., 2015). Following this, AFNI's *3dTshift* algorithm was used to perform slice-timing correction. To match spatial smoothing across MRI scanners at different sites, AFNI's 3dBlurToFWHM was used to smooth fMRI images to the smoothness level of FWHM=6mm in three directions (x, y, z)(Friedman et al., 2006). AFNI's *3dAutomask* algorithm was used to obtain a binary mask excluding non-brain voxels which was then applied to all echo planar imaging volumes prior to subsequent pipeline steps.

Neuronal tissue masking was performed using the PHYCAA+ algorithm (Churchill & Strother, 2013) to estimate task-run and subject-specific neural tissue masks. Next, nuisances regressors were calculated and regressed out from the data concurrently via general linear model (GLM). Temporal trends were modeled using a second-order Legendre polynomial basis set. Head motion effects were modeled using six subject motion parameter estimates (MPEs) obtained from the MOTCOR step. PCA was then performed on the MPEs and the 1-k principle components (PC) accounting for 85% motion variance were regressed out. Next, global signal regression was performed by regressing out the first PC from PCA analysis of the fMRI data. Finally, the task paradigm was convolved with AFNI's 'SPMG1' hemodynamic response function using

3dDeconvolve and this regressor was included in the GLM with other regressors mentioned above.

Preprocessed fMRI output files were then analysed in the same space we aligned to the Montreal Neurological Institute (MNI) template (4 mm resolution) using a two-step registration process utilizing FLS's (Jenkinson et al., 2012) FLIRT module. First, a participant's fMRI scan was aligned to their own structural T1 image. Second, the structural image was registered to the MNI template. The transformations from these steps were then combined to align each individual fMRI scan to the MNI template. First level analysis on individual runs was performed using FSL's FEAT Version 6.00. A high pass filter cut off of 100 seconds was applied to the data. Image registration was applied with a normal linear search with 3 degrees of freedom (translation only) to the standard MNI 152 T1 2 mm brain, and images were FILM prewhitened.

Scans with excessive motion were removed from the analysis based on multivariate outlier detection applied to the motion displacement parameters (see supplemental for more details).

Higher level analyses were completed with FSL's FEAT. Using mixed effects FLAME 1 design, Z (Gaussianised T/F) statistic images were thresholded non-parametrically at $Z > 2.3$ based on the recommendation in Eklund et al. (2016) and a (Bonferroni corrected) cluster significance threshold of $p = 0.007$. Behavioural and demographic data analysis was completed with SPSS 23 (IBM Corporation, 2015). Bonferroni correction for multiple comparisons was applied,

with the exception of the emotional Stroop behavioural results for congruent versus incongruent trials and incongruent adaptation (iI versus cI trials) comparisons, for which a strong directional prediction existed.

Results

A total of 145 participants were enrolled. Discovery of incidental neurological findings led to the removal of three participants, and a further 14 participants withdrew from the study or did not complete all three study visits. Runs lost due to technical difficulties, error rates greater than 30%, poor image quality or excessive motion during fMRI, or missing data equaled 36% (see Table S1). The final sample of 78 participants who completed at least one successful run at each time point (baseline, week 2 and week 8) comprised 30 HC (73% female), and 48 MDD (69% female). Only baseline data are reported here.

There were no between-group differences in distribution of sex, handedness, mean age, level of education attained, or marital status (see Table 1).

Behavioural Analyses

There were no significant between-group differences on measures of RT. Overall accuracy was significantly lower in MDD compared to HC (see Table 2).

There was a robust within-group Stroop effect for both RT and accuracy in both the MDD and HC groups (see Table 3). Incongruent adaptation was significant for the HC group only for RT. Conversely, incongruent adaptation was significant for MDD only for accuracy (see Table 3).

There were no significant differences between MDD and HC on mean accuracy and RT measures on trials with the word 'FEAR', minus trials with the word 'HAPPY', or on trials with fearful faces minus trials with happy faces.

Finally, there were no significant differences between MDD and HC on CNS-VS measures for RT, cognitive flexibility, executive functioning, or simple Stroop RT.

fMRI Analyses

Neuroimaging results are reported in Table 4. Overall, there was less activation in MDD compared to HC across *all trials* and when examining contrasts of *congruent trials*, *incongruent trials* or the *incongruent > congruent trials*. In the *incongruent > congruent trials* comparison there was lower activity in MDD compared to HC in three distinct regions: (1) right posterior division of supramarginal gyrus extending to postcentral gyrus, superior parietal lobule, and posterior division of middle temporal gyrus, and left anterior division of cingulate gyrus (see Figure 1); (2) right putamen and insular cortex; (3) left putamen and insular cortex extending to thalamus. Between group comparisons were not significant for activation to *iI > cI trials*, *fear word > happy word trials*, and *fear face > happy face trials*.

Discussion

This study explored changes in brain activation associated with performance on an fMRI emotional conflict task, examining differences between unmedicated individuals with MDD and HC.

On the Emotional Conflict Task, MDD and HC demonstrated a robust emotional Stroop effect indicated in both accuracy and RT, as has been previously reported (Chechko et al., 2009; Cheng et al., 2015; Etkin et al., 2006; Etkin & Schatzberg, 2011; Fournier et al., 2017; Wortinger et al., 2017). However, overall accuracy was lower in MDD compared to HC, in contrast to other studies that have not found group differences in accuracy or RT on an Emotional Conflict Task (Etkin et al., 2006; Fournier et al., 2017). With no significant group differences in measures of cognitive function or RT as assessed with the CNS-VS, and no group differences in RT on the Emotional Conflict Task, we suggest that poorer ability to recognize facial expressions of emotion in MDD participants is not due to a speed-accuracy trade-off or to an overall reduction in cognitive abilities.

On measures of incongruent adaptation, HC demonstrated faster RT, with no significant difference in accuracy, a pattern previously reported (Chechko et al., 2009; Etkin et al., 2006), but see also Gold et al. (2015), who did not find faster RT on iI versus cI trials in a group of 41 healthy participants. Conversely, for MDD, the expected response potentiation on the second of two consecutive incongruent trials (Etkin & Schatzberg, 2011) was reflected in accuracy scores but did not translate into the expected faster RT. Other studies have detected incongruent adaptation in accuracy but not RT in variations of emotional conflict tasks (Clayson & Larson, 2013; Krug & Carter, 2010), leading Gold et al. (2015) to consider whether incongruent adaptation necessarily involves both competence

in task execution (accuracy) and facility (RT). This suggests that in an unmedicated MDD group incongruent adaptation confers the benefit of improved competence in facial emotion recognition, without facilitated response time on the second of two consecutive incongruent trials.

In the functional imaging findings, regions engaged to a lesser degree in MDD on a number of comparisons, included the occipital fusiform gyrus, important for perception of static and dynamic facial information (Kanwisher et al., 1997; Parvizi et al., 2012), the lateral occipital cortex, important for processing structural aspects of the face and emotion recognition (Nagy et al., 2012; Pitcher et al., 2008), and the superior temporal sulcus, important for identifying dynamic facial features (Puce et al., 1998), the sum of which comprise the core neural network for face perception (Haxby et al., 2000). Greater activation in bilateral fusiform gyri, and inferior and middle occipital gyri have been associated with resolving conflict in an emotional conflict task (Chechko et al., 2012). Lower activation in regions important for face perception and for resolving emotional conflict may be associated with the overall lower accuracy observed in the MDD group.

In addition, there was lower activation in MDD compared to HC on *incongruent trials* in left planum temporale, which has been implicated in silent single word reading (Buchsbaum et al., 2005), the anterior division of the supramarginal gyrus, which may be involved in automatic reading (Stoeckel et al., 2009), the parietal operculum cortex, and the postcentral gyrus. The emergence of

the Stroop effect is contingent on interference caused by the automaticity of reading, with interference increasing as the degree of semantic relatedness between the irrelevant word and the relevant stimulus dimension increases (MacLeod, 1991). In spite of lower activation in regions important for face perception and word reading in the MDD group, a robust Stroop effect was still observed.

For the emotional Stroop contrast (*incongruent > congruent trials*), MDD patients exhibited reduced activation compared to HC in a large region encompassing right supramarginal and postcentral gyri, superior parietal lobule, anterior cingulate cortex (ACC) and the middle temporal gyrus. The ACC has been associated with processing of sensory information, and vigilance and monitoring in a colour-word Stroop task (Peterson et al., 1999). The ACC plays a key role in integrating information to regulate affect, with connections to regions important for emotion, autonomic responding, reward, and memory (Stevens et al., 2011). Further, ACC activity increases when cognitive interference requires greater behavioural adjustment (Carter et al., 2000; Sheth et al., 2012; Wilk et al., 2012), initiating top-down adaptations in cognitive control to attenuate conflict (Botvinick et al., 2004). Single cell recordings in human dorsal anterior cingulate cortex (dACC) confirm greater response at the level of individual neurons, to greater levels of cognitive interference (Sheth et al., 2012). Damage to dACC extinguishes the incongruent adaptation effect in RT, while accuracy scores remained unchanged, demonstrating that intact dACC functioning is necessary for

the preservation of incongruent adaptation (Sheth et al., 2012). This suggests that a reduction in dACC activity may be associated with difficulties integrating information from recent responses to adjust to demands of future responses. Furthermore, we also observed large regions of reduced activity in MDD on the emotional Stroop contrast encompassing bilateral putamen and insular cortex, and left thalamus, compared to HC. Insular cortex, a region often co-activated with ACC (Medford & Critchley, 2010), as is the case here, may initiate emotional awareness by combining top-down prognostic information with bottom-up stimulus-driven interoceptive information (Gu et al., 2013). In addition, the insula integrates information from the environment with visceral information from the body and is associated with overall processing of emotional information, regardless of the valence (Gogolla, 2017). The thalamus is important for relaying sensory information to the cerebral cortex (Kastner et al., 2006; McAlonan et al., 2006; Usrey & Alitto, 2015).

A number of the regions identified as less active in MDD compared to HC on the emotional Stroop comparison are recognized as part of the "limbic" ACC-basal ganglia-thalamocortical circuit (Alexander et al., 1986). Studies of functional connectivity in MDD compared to HC have indicated reduced connectivity in MDD between the nucleus accumbens and ventral rostral putamen, and subgenual ACC and ventromedial prefrontal cortex (Furman et al., 2011) and pregenual ACC and caudate nucleus (Davey et al., 2012). Additionally,

volumetric reductions have been observed in ACC, putamen, and caudate nucleus of people with MDD (Bora et al., 2012).

The most striking finding is an overall reduced level of task-related neural activity in MDD compared to HC, in addition to no between group differences in behavioural or BOLD activity to *fear > happy trials*. This suggests that patients did not show a negative bias in interpreting emotional stimuli, as some studies have observed (Bhagwagar et al., 2004; Scheele et al., 2013), but rather the overall reduced accuracy suggests a reduced sensitivity to valence in general. The emotion context insensitivity hypothesis (Rottenberg et al., 2005), posits that an overall reluctance to engage in motivated action, expressed as a hesitation to respond to or act on salient emotional cues in the external environment, regardless of their valence, may explain reduced emotional reactivity in MDD.

These findings stand in contrast to Fournier et al. (2017), who did not detect group differences in BOLD activity between unmedicated MDD and HC groups, despite having a large MDD sample size (n = 135), and Etkin and Schatzberg (2011), who observed recruitment of lateral anterior prefrontal regions in MDD. These contrasting findings can be contextualized within the framework of the National Institute of Mental Health's Research Domain Criteria initiative (RDoC), which seeks to incorporate empirical data from neuroscience and genetics into developing a cross-diagnostic classification rubric (Insel et al., 2010). Disorders such as MDD that may be unified under a specific DSM-IV category may demonstrate heterogeneous results in response to laboratory or

cognitive testing, which may be informative in identifying MDD patients with specific phenotypes for whom different treatment trajectories may be pursued (Insel et al., 2010). In light of these observations, we limit possibilities within treatment development and drug discovery with strict adherence to DSM-V clinical diagnoses (McIntyre, 2014). However, adopting the RDoC method that is domain-specific and multilateral in its approach (McIntyre, 2014) and aiming at, for example, the cognitive sub-domain of impaired emotion recognition across a series of diagnoses such as autism, Turner syndrome, Parkinson's disease, Huntington's disease, or Wilson's disease, to name a few, may be a more successful approach to driving new drug discovery and development (Fonseka et al., 2015).

Assessing emotional information processing prior to treatment begin may be helpful in predicting treatment response trajectory. Some studies have suggested that emotional information processing skills may provide the necessary cognitive framework for future changes in mood symptoms to develop (Godlewska et al., 2016; Harmer & Cowen, 2013; Tranter et al., 2009). Significant improvement in emotion recognition in MDD patients following 1 week (Shiroma et al., 2014) or 2 weeks (Tranter et al., 2009) of treatment with SSRI citalopram or 1 week of treatment with escitalopram (Godlewska et al., 2016) are correlated with clinical treatment response. The mechanism behind early improvements in emotional information processing after starting pharmacological treatment, and prior to observing changes in mood symptoms,

may involve the more immediate effects of increased levels of serotonin in the synaptic cleft, resulting in serotonin potentiation (Harmer & Cowen, 2013). Longer-term exposure to SSRIs may contribute to neuromodulation of the serotonergic system that will ameliorate mood symptoms through mechanisms such as neurogenesis in hippocampal dentate gyrus (Boldrini et al., 2012; Boldrini et al., 2009), contributing to the delayed subjective experience of improved clinical response (Harmer & Cowen, 2013). In the search for a biomarker for treatment prediction, assessing emotional information processing ability prior to treatment begin may be helpful in predicting response trajectory.

One limitation of the current study is the structure of the Emotional Conflict Task. While the colour word Stroop task is considered an example of a "cold" measure of cognition, as information processing occurs devoid of an emotional tone, the Emotional Conflict Task is an example of "hot" cognition, due to the emotional nature of the stimuli (Roiser & Sahakian, 2013), and the lack of a neutral condition. Rosier & Sahakian (2013) assert that negative thinking and expectations in MDD, as defined in the framework of Beck's cognitive model of depression (Beck, 2002), may cause individuals with MDD to cognitively ascribe "heat" or emotion to neutral stimuli or conversely, that alterations in neurotransmission in individuals with MDD may compromise bottom-up analysis of emotional stimuli. However, emotion recognition and response selection is likely to rely on both emotional and cognitive information, as these systems appear to be deeply integrated, rather than orthogonal (Pessoa, 2008).

This study examined the differences in behavioural and neural activity in unmedicated MDD and HC on an Emotional Conflict task. While both groups exhibited a robust emotional Stroop effect in both RT and accuracy measures, overall, accuracy was lower in MDD, and patients demonstrated incongruent adaption in accuracy. Patients also exhibited reduced neural activity across a number of contrasts related to Stroop performance compared to HC, suggesting an overall reduced level of sensitivity to emotionally valenced stimuli in the MDD group.

Tables and Figures

Table 1. Demographic information

Variable	MDD	HC	*Test*
Group *n*	48	30	--
Female *n* (%)	33 (69%)	22 (73%)	$X^2(1, N = 78) = 0.187$, $p = 0.666$
Right handed *n* (%)	43 (90%)	27 (90%)	$X^2(2) = 2.271$, $p = 0.321$
Age in years	34.7 ± 12.2	33.2 ± 9.8	$U = 752.5$ $z = 0.334$, $p = 0.738$
MADRS	30 ± 6	1 ± 2	$U = 1{,}440$ $z = 7.472$, $p = < 0.0005$
Length of current MDE (months)[x]	29 ± 33	--	--
Number of previous MDE[xx]	3.8 ± 3.9	--	--
Level of Education Attained (%)			
8th Grade	2%	--	$X^2(5) = 10.837$, $p = 0.055$
Grade 11/12 no diploma	6%	--	
High School Graduate/GED/Equivalent	19%	20%	
Some college	21%	7%	
Bachelor's or Associate Degree	45%	50%	
Master's /Professional/Doctoral Degree	6%	23%	
Marital Status (%)			
Never Married	50%	60%	$X^2(3) = 3.260$, $p = 0.353$
Separated/Divorced	21%	7%	
Married/Domestic Partnership	25%	30%	
Widowed	4%	3%	

Note. Unless otherwise indicated, data are reported as Mean ± SD.
MADRS. Montgomery-Åsberg Depression Rating Scale
MDE. Major Depressive Episode
[x]Data for three participants missing.
[xx]Data for four participants missing.

Table 2. Emotional Conflict Task behavioural results – between group

Comparison	**MDD***	**HC***	***Test***
Overall Accuracy	0.93	0.97	$U = 458$ $z = -2.696$, $p = 0.007$**
Accuracy Congruent Trials	0.95	0.99	$U = 487$ $z = -2.418$, $p = 0.016$
Accuracy Incongruent Trials	0.90	0.96	$U = 470.5$ $z = -2.564$, $p = 0.010$
Overall RT	709 ms	705 ms	$U = 876$ $z = 1.602$, $p = 0.109$
RT Congruent Trials	691 ms	676 ms	$U = 872$ $z = 1.561$, $p = 0.118$
RT Incongruent Trials	730 ms	724 ms	$U = 854$ $z = 1.376$, $p = 0.169$

* Data are reported as Medians

** Significant after Bonferroni correction applied.

Table 3. Emotional Conflict Task within group comparisons of emotional Stroop, and incongruent adaptation

Comparison	Congruent*	Incongruent*	Test
MDD RT	691 ms	730 ms	$z = 5.918$, $p < 0.0005$**
MDD Accuracy	0.95	0.90	$z = -4.474$, $p < 0.0005$**
HC RT	676 ms	724 ms	$z = 4.564$, $p < 0.0005$**
HC Accuracy	0.99	0.96	$z = -4.619$, $p < 0.0005$**
	cI Trials*	**iI Trials***	
MDD RT	738 ms	731 ms	$z = 0.144$, $p = 0.885$
MDD Accuracy	0.92	0.94	$z = 3.166$, $p = 0.002$**
HC RT	732 ms	707 ms	$z = -2.067$, $p = .039$**
HC Accuracy	0.94	0.97	$z = 0.875$, $p = 0.382$

* Data are reported as Medians

** Significant at $p < 0.05$

Table 4. Neuroimaging results for the comparison of MDD < HC

Comparison/ Anatomical Region	R/L	BA	MNI Coordinates			*p**	Z max	Cluster Size**
			x	y	z			
All Trials: MDD < HC								
Inferior temporal gyrus, temporooccipital part	R	37	48	-56	-8	<0.001	4.52	828
Lateral occipital cortex, inferior division		19						
Lateral occipital cortex, superior division		19						
Occipital fusiform gyrus		-						
Congruent: MDD < HC								
Inferior temporal gyrus, temporooccipital part	R	37	48	-56	-8	0.00253	4.07	704
Lateral occipital cortex, inferior division		19						
Lateral occipital cortex, superior division		19						
Occipital fusiform gyrus		-						
Incongruent: MDD < HC								
Inferior temporal gyrus, temporooccipital part	R	37	48	-56	-8	<0.001	4.57	1376
Lateral occipital cortex, inferior division		19						
Lateral occipital cortex, superior division								
Planum temporale	L	22	-46	-42	16	0.00583	4.12	616
Supramarginal gyrus, anterior division		40						
Parietal operculum cortex		-						
Postcentral gyrus		40						

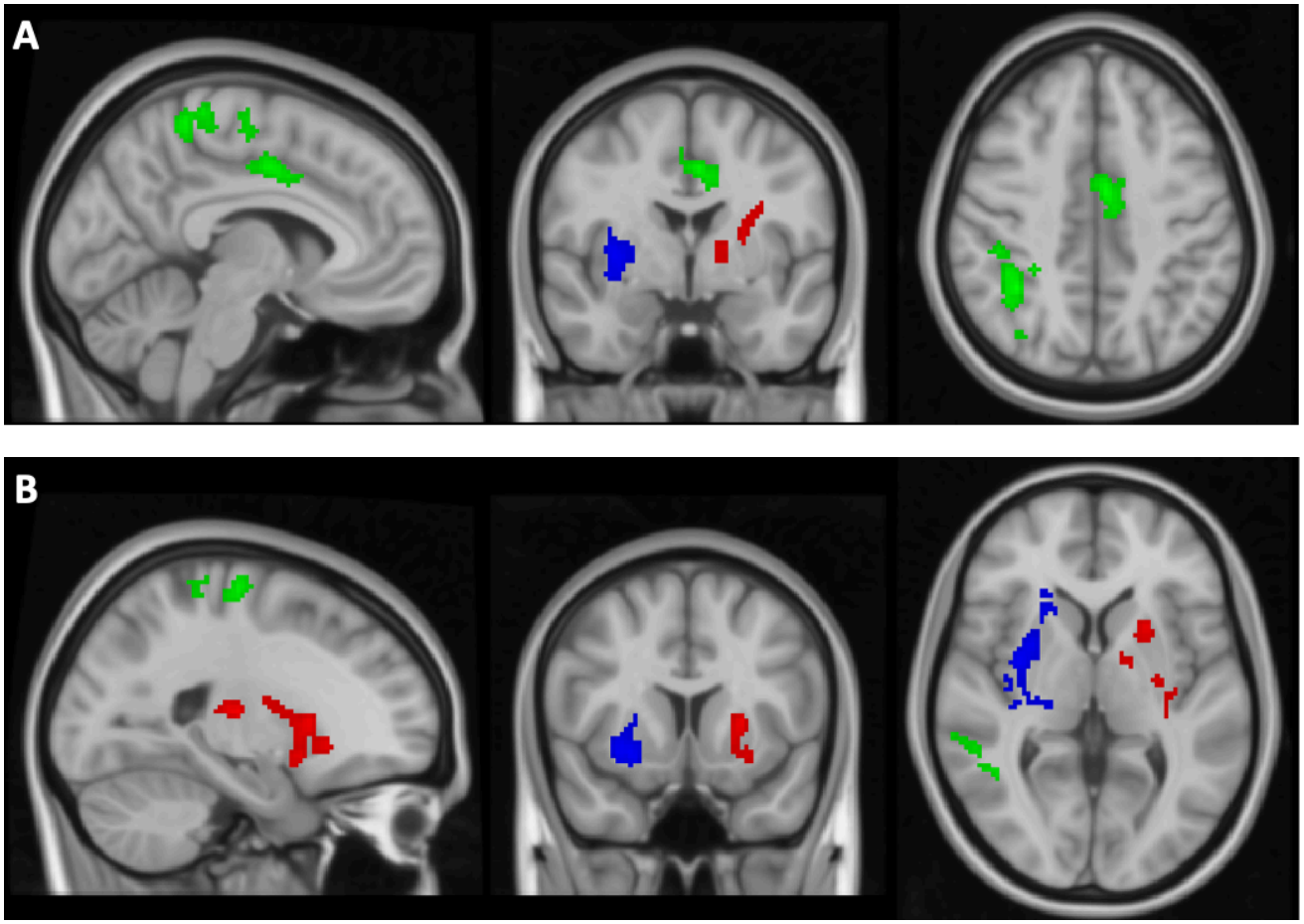
Table 4. (Continued)

Comparison/ Anatomical Region	R/L	BA	MNI Coordinates			*p**	Z max	Cluster Size**
			x	y	z			
Incongruent > Congruent:								
MDD < HC								
Supramarginal gyrus, posterior division	R	-	38	-44	38	<0.001	3.75	2974
Postcentral gyrus		-						
Superior parietal lobule		39,7						
Cingulate gyrus, anterior division		24						
Middle temporal gyrus, posterior division		21						
Putamen	R	49	32	8	-8	<0.001	3.44	1180
Insular Cortex		-						
Insular cortex	L	13	-34	-20	10	0.00617	3.70	729
Putamen		49						
Thalamus		50						

R/L = Right/Left; BA = Brodmann Area

*Significant after Bonferroni correction applied

** Expressed in voxels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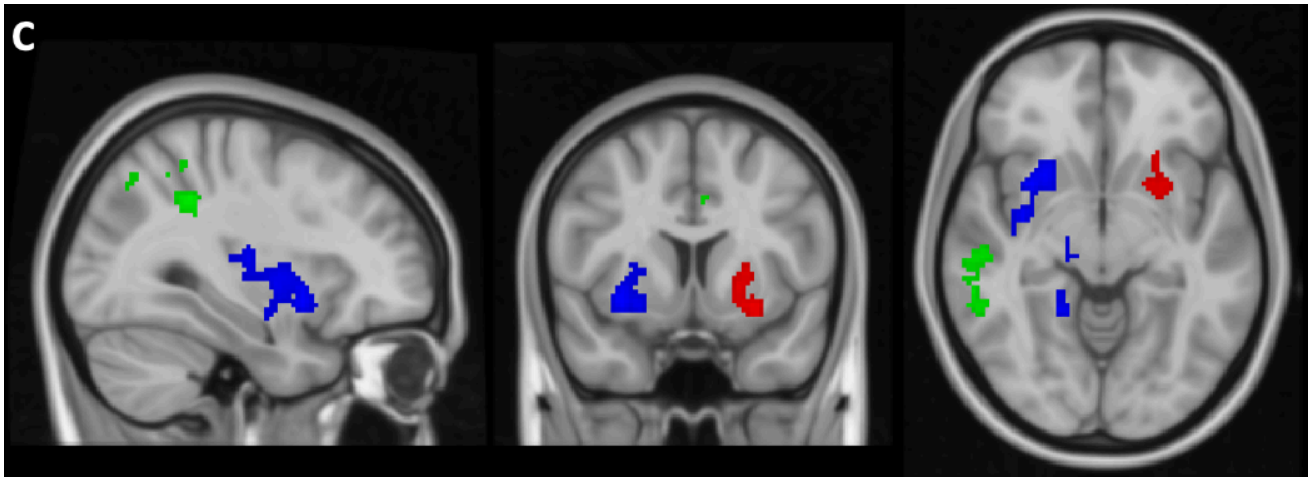

Figure 1. Incongruent > Congruent: MDD < HC

Image is projected on the MNI 152 T1 1 mm standard brain and presented in radiological convention. Images were thresholded non-parametrically using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.007$. There are 3 separate contiguous clusters pictured above. As listed in Table 4, green refers to right posterior division of supramarginal gyrus, postcentral gyrus, superior parietal lobule, anterior cingulate gyrus, and posterior middle temporal gyrus; blue refers to right putamen and insular cortex; red refers to left insular cortex, putamen and thalamus. MNI coordinates for each image are as follows: A) (x = -6, y = -2, z = 43), B) (x = -22, y = 10, z = 3), C) (x = 32, y = 8, z = -7).

Supplementary Material

Table S1. Reasons for runs being excluded from the Emotional Conflict Task, by grouping, and run number.

	Grouping				
	MDD		Control		
Exclusion Criteria	**Run 1**	**Run 2**	**Run 1**	**Run 2**	**TOTAL (%)**
Runs Completed	73	73	55	55	256 (100%)
Missing/corrupted behavioural data	1	-	8	7	16 (6%)
Missing/corrupted/poor quality fMRI data	13	23	12	15	63 (25%)
Too many errors in behavioural data	5	5	3	1	14 (5%)
Usable Runs	54	45	32	32	163 (64%)
Runs Included in Final Analysis*	45	37	24	26	132 (52%)

* Includes only runs for participants that had completed at least one usable run at each time point (baseline, week 2 and week 8). Only baseline data are examined in this paper.

Table S2. Scanning protocol deviations

Site	Scanning Protocol Deviation
Philips site	Scanned with a 1 mm inter-slice gap
	Used a flip angle of 90º
Siemens site	Used TE = 25 ms
One GE Discovery site	Scanned without parallel imaging acceleration

Multivariate Outlier Detection

To detect scans corrupted by motion, the average of each of the six rigid-body motion parameter estimates was calculated for each time-series. Three multivariate outlier detection techniques were then applied to the six mean motion parameters from each site. The outlier detection methods included: 1) a FAST-MCD (minimum covariance determinant) [203]; 2) a bootstrap version of MCD using "component score" distance; and 3) a bootstrap version of MCD using Mahalanobis distance. These algorithms flagged any scans whose mean motion was away from the distribution mean in any direction. Thus, participants could also be flagged when having minimal motion compared to the rest of the scans from a particular site. To address this, results of outlier detection techniques were combined with a *total-displacement* (TD) value calculated based on the 6 motion parameters for each scan:

$$TD = \sqrt{(d_x + 75r)^2 + \left(d_y + 75y\right)^2 + (d_z + 75p)^2}$$

Where d_x, d_y and d_z are displacements on the right-left, anterior-posterior and interior-superior axes respectively, and roll (r), yaw (y) and pitch (p), with values in radians, respectively.

The decision to remove a particular scan from further analysis was based on the following criteria: 1) a scan was flagged by at least two outlier detection methods and TD of the scan was ≥ 1 SD of the mean TD for all sites, or, 2) a scan was flagged by one outlier detection method and TD of the scan was > 2 SD of the mean TD for the entire sample.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci,* 9, 357-381. doi:10.1146/annurev.ne.09.030186.002041

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).*

Beck, A. T. (2002). Cognitive models of depression. In R. L. Leahy & E. T. Dowd (Eds.), *Clinical Advances in Cognitive Psychotherapy: Theory and Application* (pp. 29-61): Springer Publishing Company.

Bhagwagar, Z., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2004). Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. *Am J Psychiatry,* 161, 166-168. doi:10.1176/appi.ajp.161.1.166

Boldrini, M., Hen, R., Underwood, M. D., Rosoklija, G. B., Dwork, A. J., Mann, J. J., & Arango, V. (2012). Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in Major Depression. *Biol Psychiatry,* 72(7), 562-571. doi:10.1016/j.biopsych.2012.04.024

Boldrini, M., Underwood, M. D., Hen, R., Rosoklija, G. B., Dwork, A. J., John Mann, J., & Arango, V. (2009). Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology,* 34(11), 2376-2389. doi:10.1038/npp.2009.75

Bora, E., Harrison, B. J., Davey, C. G., Yucel, M., & Pantelis, C. (2012). Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in Major Depressive Disorder. *Psychol Med,* 42(4), 671-681. doi:10.1017/S0033291711001668

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci,* 8(12), 539-546. doi:10.1016/j.tics.2004.10.003

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in Major Depression: a review. *Aust N Z J Psychiatry,* 44, 681-696. doi:10.3109/00048674.2010.496359

Buchsbaum, B. R., Olsen, R. K., Koch, P. F., Kohn, P., Kippenhan, J. S., & Berman, K. F. (2005). Reading, hearing, and the planum temporale. *Neuroimage,* 24(2), 444-454. doi:10.1016/j.neuroimage.2004.08.025

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in Major Depressive Disorder. *Clin Psychol Rev,* 28(4), 676-691. doi:10.1016/j.cpr.2007.10.001

Campbell, K. L., Grigg, O., Saverino, C., Churchill, N., & Grady, C. L. (2013). Age differences in the intrinsic functional connectivity of default network subsystems. *Front Aging Neurosci,* 5, 1-12. doi:10.3389/fnagi.2013.00073

Carter, C. S., Macdonald, A. M., Botvinick, M., Ross, L. L., Stenger, A., Noll, D., & Cohen, J. D. (2000). Parsing executive processes: Strategic vs. evaluative functions in the anterior cingulate cortex. *PNAS,* 97(4), 1944-1948. doi:10.1073/pnas.97.4.1944

Chechko, N., Kellermann, T., Zvyagintsev, M., Augustin, M., Schneider, F., & Habel, U. (2012). Brain circuitries involved in semantic interference by demands of emotional and non-emotional distractors. *PLoS One,* 7(5), e38155. doi:10.1371/journal.pone.0038155

Chechko, N., Wehrle, R., Erhardt, A., Holsboer, F., Czisch, M., & Samann, P. G. (2009). Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder. *PLoS One,* 4(5), e5537. doi:10.1371/journal.pone.0005537

Cheng, P., Preston, S. D., Jonides, J., Mohr, A. H., Thummala, K., Casement, M., . . . Deldin, P. J. (2015). Evidence against mood-congruent attentional bias in Major Depressive Disorder. *Psychiatry Res,* 230(2), 496-505. doi:10.1016/j.psychres.2015.09.043

Churchill, N. W., Spring, R., Afshin-Pour, B., Dong, F., & Strother, S. C. (2015). An automated, adaptive framework for optimizing preprocessing pipelines in task-based functional MRI. *PLoS One,* 10(7), e0131520. doi:10.1371/journal.pone.0131520

Churchill, N. W., & Strother, S. C. (2013). PHYCAA+: an optimized, adaptive procedure for measuring and controlling physiological noise in BOLD fMRI. *Neuroimage,* 82, 306-325. doi:10.1016/j.neuroimage.2013.05.102

Clayson, P. E., & Larson, M. J. (2013). Adaptation to emotional conflict: evidence from a novel face emotion paradigm. *PLoS One,* 8(9), e75776. doi:10.1371/journal.pone.0075776

Cox, R. W. (1996). AFNI: software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Comput Biomed Res,* 29, 162-173. doi:10.1006/cbmr.1996.0014

Dalili, M. N., Penton-Voak, I. S., Harmer, C. J., & Munafò, M. R. (2015). Meta-analysis of emotion recognition deficits in Major Depressive Disorder. *Psychol Med*, 1135-1144. doi:10.1017/S0033291714002591

Darwin, C. (1872). *The expression of the emotions in man and animals*. London, UK: John Murray.

Davey, C. G., Harrison, B. J., Yucel, M., & Allen, N. B. (2012). Regionally specific alterations in functional connectivity of the anterior cingulate cortex in Major Depressive Disorder. *Psychol Med,* 42(10), 2071-2081. doi:10.1017/S0033291712000323

Davidson, R. J., Irwin, W. I., Anderle, M. J., & Kalin, N. H. (2003). The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am J Psychiatry,* 160, 64-75. doi:10.1176/appi.ajp.160.1.64

Duque, A., & Vazquez, C. (2015). Double attention bias for positive and negative emotional faces in clinical depression: evidence from an eye-tracking study. *J Behav Ther Exp Psychiatry,* 46, 107-114. doi:10.1016/j.jbtep.2014.09.005

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *PNAS,* 113(28), 7900-7905. doi:10.1073/pnas.1602413113

Ekman, P., & Friesen, W. V. (1976). Pictures of Facial Affect: Consulting Psychologists Press.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron,* 51(6), 871-882. doi:10.1016/j.neuron.2006.07.029

Etkin, A., & Schatzberg, A. F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in Generalized Anxiety and Major Depressive Disorders. *Am J Psychiatry,* 168(9), 968-978. doi:10.1176/appi.ajp.2011.10091290

Favre, P., Polosan, M., Pichat, C., Bougerol, T., & Baciu, M. (2015). Cerebral correlates of abnormal emotion conflict processing in euthymic bipolar patients: a functional MRI study. *PLoS One,* 10(8), e0134961-0134916. doi:10.1371/journal.pone.0134961

Fonseka, T. M., McIntyre, R. S., Soczynska, J. K., & Kennedy, S. H. (2015). Novel investigational drugs targeting IL-6 signaling for the treatment of depression. *Expert Opin Investig Drugs,* 24(4), 459-475. doi:10.1517/13543784.2014.998334

Fournier, J., Chase, H., Greenberg, T., Etkin, A., Almeida, J., Stiffler, R., . . . Phillips, M. (2017). Neuroticism and individual differences in neural function in unmedicated Major Depression: findings from the EMBARC study. *Biol Psychiatry Cogn Neurosci Neuroimaging,* 2(2), 138-148. doi:10.1016/j.bpsc

Frey, B. N., Hall, G. B., Attard, S., Yucel, K., Skelin, I., Steiner, M., & Soares, C. N. (2010). Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point? *Menopause,* 17(4), 840-845. doi:10.1097/gme.0b013e3181df840f

Friedman, L., Glover, G. H., Krenz, D., & Magnotta, V. (2006). Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. *Neuroimage,* 32(4), 1656-1668. doi:10.1016/j.neuroimage.2006.03.062

Furman, D. J., Hamilton, J. P., & Gotlib, I. H. (2011). Frontostriatal functional connectivity in Major Depressive Disorder. *Biol Mood Anxiety Disord,* 1(11), 1-10. doi:10.1186/2045-5380-1-11

Godlewska, B. R., Browning, M., Norbury, R., Cowen, P. J., & Harmer, C. J. (2016). Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Transl Psychiatry,* 6(11), e957. doi:10.1038/tp.2016.130

Gogolla, N. (2017). The insular cortex. *Curr Biol,* 27(12), R580-R586. doi:10.1016/j.cub.2017.05.010

Gold, A. L., Jarcho, J. M., Rosen, D. K., Pine, D. S., & Ernst, M. (2015). Emotional and nonemotional conflict processing in pediatric and adult anxiety disorders. *J Child Adolesc Psychopharmacol,* 25(10), 754-763. doi:10.1089/cap.2015.0066

Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. *J Comp Neurol,* 521(15), 3371-3388. doi:10.1002/cne.23368

Gualtieri, C. T., & Johnson, L. G. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol,* 21(7), 623-643. doi:10.1016/j.acn.2006.05.007

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci,* 368(1615), 20120407. doi:10.1098/rstb.2012.0407

Haxby, J., Hoffman, E., & Gobbini, M. (2000). The distributed human neural system for face perception. *Trends Cogn Sci,* 4(6), 223-233. doi:10.1016/S1364-6613(00)01482-0

Hill, A. B., & Knowles, T. H. (1991). Depression and the 'emotional' Stroop effect. *Person Individ Diff,* 12(5), 481-485. doi:10.1016/0191-8869(91)90066-K

IBM Corporation. (2015). IBM SPSS Statistics for Macintosh, Version 23.0 (Version 23.0). Armonk, NY, USA: IBM Corporation.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Doman Criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry,* 167(7), 748-751. doi:10.1176/appi.ajp.2010.09091379

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

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci,* 17(11), 4302-4311. doi:10.1523/JNEUROSCI.17-11-04302.1997

Kastner, S., Schneider, K. A., & Wunderlich, K. (2006). Beyond a relay nucleus: neuroimaging views on the human LGN. *Prog Brain Res,* 155, 125-143. doi:10.1016/s0079-6123(06)55008-3

Kennedy, S. H., Lam, R. W., Rotzinger, S., Milev, R. V., Blier, P., Downar, J., . . . on behalf of the CAN-BIND Investigator Team. (2019). Symptomatic and functional outcomes and early prediction of response to escitalopram monotherapy and sequential adjunctive aripiprazole therapy in patients with Major Depressive Disorder. *J Clin Psychiatry,* 80(2), e1-e10. doi:10.4088/JCP.18m12202

Krug, M. K., & Carter, C. S. (2010). Adding fear to conflict: a general purpose cognitive control network is modulated by trait anxiety. *Cogn Affect Behav Neurosci,* 10(3), 357-371. doi:10.3758/CABN.10.3.357

Lam, R. W., Milev, R., Rotzinger, S., Andreazza, A. C., Blier, P., Brenner, C., . . . and on behalf of the CAN-BIND Investigator Team. (2016). Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. *BMC Psychiatry,* 16(1), 105. doi:10.1186/s12888-016-0785-x

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: an integrative review. *Psychological bulletin,* 109(2), 163-203. doi:10.1037/0033-2909.109.2.163

MacQueen, G. M., Hassel, S., Arnott, S. R., Jean, A., Bowie, C. R., Bray, S. L., . . . on behalf of the CAN-BIND Investigator Team. (2019). The Canadian Biomarker Integration Network in Depression (CAN-BIND): magnetic resonance imaging protocols. *J Psychiatry Neurosci,* 44(3), 1-14. doi:10.1503/jpn.180036

McAlonan, K., Cavanaugh, J., & Wurtz, R. H. (2006). Attentional modulation of thalamic reticular neurons. *J Neurosci,* 26(16), 4444-4450. doi:10.1523/jneurosci.5602-05.2006

McIntyre, R. S. (2014). A vision for drug discovery and development: novel targets and multilateral partnerships. *Adv Ther,* 31(3), 245-246. doi:10.1007/s12325-014-0105-0

Medford, N., & Critchley, H. D. (2010). Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. *Brain Struct Funct,* 214(5-6), 535-549. doi:10.1007/s00429-010-0265-x

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *Brit J Psychiat,* 134, 382-389. doi:10.1192/bjp.134.4.382

Nagy, K., Greenlee, M. W., & Kovacs, G. (2012). The lateral occipital cortex in the face perception network: an effective connectivity study. *Front Psychol,* 3, 141. doi:10.3389/fpsyg.2012.00141

Parvizi, J., Jacques, C., Foster, B. L., Witthoft, N., Rangarajan, V., Weiner, K. S., & Grill-Spector, K. (2012). Electrical stimulation of human fusiform face-

selective regions distorts face perception. *J Neurosci,* 32(43), 14915-14920. doi:10.1523/JNEUROSCI.2609-12.2012

Peckham, A. D., McHugh, R. K., & Otto, M. W. (2010). A meta-analysis of the magnitude of biased attention in depression. *Depress Anxiety,* 27(12), 1135-1142. doi:10.1002/da.20755

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat Rev Neurosci,* 9(2), 145-158. doi:10.1038/nrn2317

Peterson, B. S., Skudlarski, P., Gatenby, J. C., Zhang, H., Anderson, A. W., & Gore, J. C. (1999). An fMRI study of Stroop word-color interference: evidence for cinguate subregions subserving multiple distributed attentional systems. *Biol Psychiatry,* 45, 1237-1258. doi:10.1016/S0006-3223(99)00056-6

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J Neurosci,* 28(36), 8929-8933. doi:10.1523/JNEUROSCI.1450-08.2008

Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *J Neurosci,* 18(6), 2188-2199. doi:10.1523/JNEUROSCI.14-03-01450.1994

Rey, G., Desseilles, M., Favre, S., Dayer, A., Piguet, C., Aubry, J.-M., & Vuilleumier, P. (2014). Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: preliminary findings from a follow-up state-based fMRI study. *Psychiatry Res,* 223(2), 84-93. doi:10.1016/j.pscychresns.2014.04.016

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS Spectrums,* 18(3), 139-149. doi:10.1017/S1092852913000072

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in Major Depressive Disorder. *J Abnorm Psychol,* 114(4), 627-639. doi:10.1037/0021-843X.114.4.627

Rousseeuw, P. J., & Van Driessen, K. (1999). A fast algorithm for the minimum covariance determinant estimator. *Technometrics,* 41(3), 212-223. doi:10.1080/00401706.1999.10485670

Rubinow, D. R., & Post, R. M. (1992). Impaired recognition of affect in facial expression in depressed patients. *Biol Psychiatry,* 31(9), 947-953. doi:10.1016/0006-3223(92)90120-O

Scheele, D., Mihov, Y., Schwederski, O., Maier, W., & Hurlemann, R. (2013). A negative emotional and economic judgment bias in Major Depression. *Eur Arch Psychiatry Clin Neurosci,* 263(8), 675-683. doi:10.1007/s00406-013-0392-5

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-Prime User's Guide* (2.0 ed.). Pittsburgh: Psychology Software Tools, Inc.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry,* 59 Suppl 20, 22-57. doi:10.1016/S0924-9338(97)83296-8

Sheth, S. A., Mian, M. K., Patel, S. R., Asaad, W. F., Williams, Z. M., Dougherty, D. D., . . . Eskandar, E. N. (2012). Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature,* 488(7410), 218-221. doi:10.1038/nature11239

Shiroma, P. R., Thuras, P., Johns, B., & Lim, K. O. (2014). Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiatry,* 29(11), 1132-1139. doi:10.1002/gps.4104

Stevens, F. L., Hurley, R. A., & Taber, K. H. (2011). Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci,* 23(2), 121-125. doi:10.1176/appi.neuropsych.23.2.121

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex,* 45(9), 1091-1096. doi:10.1016/j.cortex.2008.12.004

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J Exp Psychol,* 18, 643-662. doi:10.1037/h0054651

Strother, S. C. (2006). Evaluating fMRI preprocessing pipelines. *IEEE Eng Med Biol Mag,* 25(2), 27-41. doi:10.1109/MEMB.2006.1607667

Torres-Quesada, M., Korb, F. M., Funes, M. J., Lupiáñez, J., & Egner, T. (2014). Comparing neural substrates of emotional vs. non-emotional conflict

modulation by global control context. *Front Hum Neurosci,* 8, 1-14. doi:10.3389/fnhum.2014.00066

Tranter, R., Bell, D., Gutting, P., Harmer, C., Healy, D., & Anderson, I. M. (2009). The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. *J Affect Disord,* 118(1-3), 87-93. doi:10.1016/j.jad.2009.01.028

Usrey, W. M., & Alitto, H. J. (2015). Visual functions of the thalamus. *Annu Rev Vis Sci,* 1, 351-371. doi:10.1146/annurev-vision-082114-035920

Wilk, H. A., Ezekiel, F., & Morton, J. B. (2012). Brain regions associated with moment-to-moment adjustments in control and stable task-set maintenance. *Neuroimage,* 59(2), 1960-1967. doi:10.1016/j.neuroimage.2011.09.011

Wortinger, L. A., Endestad, T., Melinder, A. M., Oie, M. G., Sulheim, D., Fagermoen, E., & Wyller, V. B. (2017). Emotional conflict processing in adolescent chronic fatigue syndrome: a pilot study using functional magnetic resonance imaging. *J Clin Exp Neuropsychol,* 39(4), 355-368. doi:10.1080/13803395.2016.1230180

Chapter 5

Escitalopram Ameliorates Differences in Neural Activity Between Healthy Comparison and Major Depressive Disorder Groups on an fMRI Emotional Conflict Task: A CAN-BIND Report

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Abstract

Background: Identifying objective biomarkers can assist in predicting remission/non-remission to a given treatment, improving remission rates, and reducing illness burden.

Methods: Sixteen MDD 8-week remitters (MDD-8), twelve 16-week remitters (MDD-16), 14 non-remitters (MDD-NR) and 30 healthy comparison participants (HC) completed a functional magnetic resonance imaging emotional conflict task at baseline, prior to treatment with escitalopram, and 8 weeks after treatment initiation. Patients were followed 16 weeks to assess remitter status.

Results: All groups demonstrated emotional Stroop in reaction time (RT) at baseline and Week 8. There were no baseline differences between HC and MDD-16 or MDD-NR in RT or accuracy. By Week 8, MDD-8 demonstrated poorer accuracy compared to HC. Compared to HC, the baseline blood-oxygen level dependent (BOLD) signal was decreased in MDD-8 in brain-stem and thalamus; in MDD-16 in lateral occipital cortex, middle temporal gyrus, and cuneal cortex; in MDD-NR in lingual and occipital fusiform gyri, thalamus, putamen, caudate, cingulate gyrus, insular cortex, cuneal cortex, and middle temporal gyrus. By Week 8, there were no BOLD activity differences between MDD groups and HC.

Limitations: The Emotional Conflict Task lacks a neutral (non-emotional) condition, restricting interpretation of how mood may influence perception of non-emotionally valenced stimuli.

Conclusions: The Emotional Conflict Task is not an objective biomarker for remission trajectory in patients with MDD receiving escitalopram treatment. Escitalopram may have influenced emotion recognition in MDD groups in terms of decreased accuracy and BOLD signal in response to an Emotional Conflict Task, following 8 weeks of escitalopram treatment.

Key Words: major depressive disorder, emotion recognition, emotional Stroop, fMRI, emotional conflict, escitalopram

Introduction

Major depressive disorder (MDD) is projected to be the leading global burden of disease across both sexes by 2030 (World Health Organization, 2008). Presently, there is no reliable method of predicting who will achieve remission or response to a specific antidepressant (Kudlow et al., 2012). A current research priority is to identify objective biomarkers that may subtype individuals with MDD based on likelihood of achieving remission/non-remission to a given treatment. Such biomarkers could ultimately reduce the treatment steps required to reach remission, while improving remission rates, reducing the burden of MDD on patients, caregivers, and the healthcare system.

From the patient point of view, remission provides a greater opportunity to enhance functioning (Kennedy, 2002). Patients achieving only partial remission are more likely to experience significant difficulties in occupational and social functioning (Romera et al., 2010), and have a greater risk of recurrence or relapse (Paykel, 2008; Paykel et al., 1995), compared to patients who achieve complete remission.

The ability to correctly perceive and understand emotional information is essential for healthy social functioning (Blair, 2003; Darwin, 1872). Impaired ability to interpret facial expressions has been associated with poorer relationships and increased feelings of depression (Carton et al., 1999). Many studies report evidence of a mood-congruent bias in emotional information processing in MDD, with heightened attenuation or decreased responsivity for positive emotional

stimuli and a negative potentiation or increased responsivity to negative stimuli (Bouhuys et al., 1999; Bourke et al., 2010; Gotlib et al., 2011; Stuhrmann et al., 2011). Some reports indicate patients with MDD express an overall attenuated response to a range of emotional stimuli, irrespective of valence (Bylsma et al., 2008; Imbault & Kuperman, 2018; Rottenberg et al., 2005) or patients with MDD have difficulty inhibiting responses to negatively valenced information or disengaging from it (Gotlib & Joormann, 2010), even when in remission (Vanderhasselt et al., 2012).

To examine whether differences in emotional information processing predict different remission rates in MDD, we employed an Emotional Conflict Task (Etkin et al., 2006). This task is constructed from images of fearful or happy faces with a congruent or incongruent emotional word label superimposed across the face. The task requires participants to ignore emotional task-irrelevant information (the printed name of an emotion) and identify, emotional task-relevant information (the affect expressed on the face). Slower reaction time (RT) on incongruent compared to congruent trials is recognized as the emotional Stroop effect (Hill & Knowles, 1991), and studies measuring accuracy have reported decreased accuracy on incongruent compared to congruent trials (Etkin et al., 2006; Favre et al., 2015; Fournier et al., 2017; Rey et al., 2014; Torres-Quesada et al., 2014).

To evaluate baseline task-based differences between HC and 8-week remitters (MDD-8), 16-week remitters (MDD-16) and non-remitters (MDD-NR)

on the Emotional Conflict Task, we compared groups on the Emotional Conflict Task. We expected all groups to demonstrate the emotional Stroop effect in both RT and accuracy, given the robust nature of the task. We also expected overall accuracy rates to be lower in MDD groups compared to HC, based on impaired emotion recognition in MDD (Dalili et al., 2015; Rubinow & Post, 1992). Furthermore, we expected slower RT in the MDD-NR compared to HC, based on previous work identifying psychomotor slowing as a predictor of treatment non-response to SSRI fluoxetine (Taylor et al., 2006). Decreased accuracy has also been shown in a Non-Responder group on both incongruent and congruent trials in a colour word Stroop task (Xue et al., 2017). Thus, we expected lower accuracy in the MDD-NR group on both *congruent* and *incongruent trials*, compared to HC. Comparing patterns of neural response, we hypothesized that response differences on *congruent*, *incongruent*, and *incongruent* > *congruent trials*, would distinguish between HC, and MDD-8, MDD-16 and MDD-NR groups at baseline. Previous findings of rostral cingulate hypometabolism in MDD treatment non-responders and hypermetabolism in treatment responders in a positron emission tomography study (Mayberg et al., 1997), predicted there would be similar differences in BOLD cingulate activity between HC and MDD-8/-16 and MDD-NR groups, respectively.

A secondary objective was to examine within-group changes in behavioural responding and BOLD activity induced by escitalopram at Week 8. Within each group, we expected to observe a preserved emotional Stroop across

time. In MDD groups, we expected changes in observed BOLD activity in response to escitalopram, due to the early positive effects of an SSRI on emotional information processing (Harmer & Cowen, 2013). Between groups, we expected MDD-8 neural activity would more closely approximate that of HC by Week 8, while neural and behavioural responses in MDD-16 and MDD-NR would not.

Finally, to identify differences in participants responding to escitalopram after 8 weeks of treatment, compared to participants that would respond with the later addition of aripiprazole we compared MDD-8 and MDD-16 at Week 8.

Materials and Methods

This research was conducted within the framework of the Canadian Biomarker Integration Network for Depression (CAN-BIND-1) (Kennedy et al., 2019; Lam et al., 2016; MacQueen et al., 2019).

Participants

Participants enrolled at six Canadian academic health science institutions in the CAN-BIND-1 study (Kennedy et al., 2019) who completed the Emotional Conflict Task, totaled 59 HC and 86 MDD. Institutional ethics boards at each site approved the study. Inclusion criteria for MDD were: between 18 and 60 years of age, meeting criteria for a major depressive episode (MDE) as determined by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and as defined in the Diagnostic and Statistical Manual IV-TR (American Psychiatric Association, 2000) the episode was ≤ 3 months in duration, with a score ≥ 24 on

the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), patients were psychotropic medication free for ≤ 5 half-lives at baseline testing, and fluent in English. Exclusion criteria for MDD were: psychosis in current MDE, bipolar I/II diagnosis, failure of ≥ four pharmacological interventions, high risk for hypomanic switch, previous non-response/intolerance to aripiprazole or escitalopram, initiation of psychological treatment in ≤ 3 months with intention to continue treatment, other primary psychiatric diagnoses, personality disorder that would interfere with study completion (as determined by clinician), or high suicide risk. Exclusion criteria for all participants included breastfeeding/pregnancy, substance dependence/abuse in previous 6 months, significant head trauma/neurological disorder, other non-stabilized medical conditions, or any MRI contraindications. All participants provided written informed consent and received compensation for study participation.

Data were collected at baseline (prior to starting pharmacotherapy), 2 weeks, and 8 weeks after starting pharmacotherapy. HC were tested at these same intervals without medication. To determine treatment remission status, MDD participants were followed for 16 weeks. As Emotional Conflict Task data were collected over two consecutive runs at each time point (baseline, Week 2 and Week 8), if at least one run at each time point was deemed valid, data for that participant were included in the analysis.

The MDD sample was classified into the following groups: patients demonstrating a ≤ 10 MADRS by Week 8 (Hawley et al., 2002; Mendlewicz, 2008), which they maintained at week 16, were defined as the 8 week remitter group (MDD-8); patients who, with addition of adjunctive aripiprazole commencing after Week 8 testing, demonstrated a MADRS score of ≤ 10 by week 16, were defined as the 16 week remitter group (MDD-16); patients maintaining a MADRS score > 10 at both weeks 8 and 16, with adjunctive treatment with aripiprazole after Week 8 testing, were defined as MDD non-remitters (MDD-NR).

Procedures

Demographic, diagnostic, and medical history information was acquired through interviews and standardized self-report questionnaires (for additional details see Kennedy et al., 2019; Lam et al., 2016; MacQueen et al., 2019). The MADRS (Montgomery & Åsberg, 1979) was used to assess depressive symptom severity.

Treatment

Following the baseline visit, patients started escitalopram treatment at 10 mg/d with the option of increased dosages at Week 2 and at three follow up visits, up to 20 mg/d (for more details, see Lam et al., 2016). Patients attaining a > 50% reduction in baseline MADRS score (study defined criteria for treatment response) by Week 8 continued with escitalopram treatment for an additional 8 weeks; patients who did not meet this Week 8 criteria, received adjunctive

treatment with aripiprazole starting at 2 mg/d flexible dosage up to 10 mg/d according to physician judgement.

fMRI Task

Sequence and parameters of the Emotional Conflict Task were informed by a previous fMRI publication from our group (Frey et al., 2010). The task features 148 black and white images of happy or fearful faces (Ekman & Friesen, 1976) cropped to remove hair and neck. Centered below the bridge of the nose, the word "HAPPY" or "FEAR" in red upper case lettering is superimposed on the respective images, such that it is either congruent (face affect and word match) or incongruent (face affect and word do not match) (for additional details see Etkin & Schatzberg, 2011; Frey et al., 2010). Equal numbers of congruent and incongruent trials were counterbalanced and presented in two separate runs. Each run comprised 74 stimuli with a duration of 6 minutes 35 seconds.

To ensure task comprehension, prior to the experiment, participants practiced the task on a computer outside of the scanner. They were instructed to identify the affect of the face as quickly and accurately as possible, and to ignore the word superimposed on the face. Images were presented to participants in the MRI scanner with E-Prime software version 2 (Schneider et al., 2002). On each trial, the stimulus was presented for 1 second, followed by a jittered mean inter-stimulus interval of 4 seconds (range of 3 to 5 seconds) during which a centered fixation cross was displayed to participants. Slower RT and decreased accuracy on incongruent compared to congruent trials, is defined as the emotional Stroop

effect. The maximum error of commission rate was 25% per run, with an overall maximum error rate (errors of omission and commission) of 30%. For accuracy calculations, trials with RT > 2 SD from trial type mean were retained. The accuracy calculation formula:

$$\%\ correct\ \text{trial type} = \frac{1 - (\text{trial type errors})}{(\text{number of events for trial type})}$$

For RT analysis, error trials, and trials with RT > 2 standard deviations above or below the trial-type mean were removed. Neuroimaging analyses of *congruent*, *incongruent*, and *incongruent* > *congruent*, did not include error trials, whereas the *all trials* analysis did.

fMRI Data Acquisition

Images were acquired using multi-channel receiver head coils on five 3T whole-body MRI scanners (one Tim Trio from Siemens, Germany; one Intera Achieva from Philips, Netherlands; one Signa HDxt and two Discovery MR 750 from GE Healthcare, USA). Whole-head fMRI images were acquired using 4.0 mm isotropic voxels with a T_2^*-weighted single-shot echo-planar gradient echo imaging sequence: FOV=256×256 mm; matrix=64×64; 36–40 4 mm oblique slices with no gap; TR=2000 ms, TE = 30 ms, flip angle=75º; parallel imaging R=2. For the Emotional Conflict Task, 188 volumes per run were acquired, with two runs per session (total scan time 12.5 minutes). Acquisition parameter deviations at individual sites are listed in Table S1.

FMRI data preprocessing was completed with the software package Optimization of Preprocessing Pipelines for NeuroImaging-fMRI (OPPNI) (Churchill et al., 2015; Strother, 2006), and steps are summarized here. To identify the volume with the smallest Euclidean distance from the median coordinates in principal component analysis (PCA) space, considered as the volume with the least head displacement, PCA was applied to the 4D fMRI data. This became the reference volume for the Motion Correction (MOTCOR) step. Using AFNI's (Cox, 1996) 3dvolreg algorithm rigid-body MOTCOR was applied transforming each 4D image to match the volume with least head displacement. Outlier brain volumes were removed and replaced with interpolated values from adjacent volumes (Campbell et al., 2013; Churchill et al., 2015). AFNI's *3dTshift* algorithm was used for slice-timing correction. To match spatial smoothing across different MRI scanners AFNI's 3dBlurToFWHM was used to smooth fMRI images FWHM=6mm in three directions (x, y, z) (Friedman et al., 2006). Using AFNI's *3dAutomask,* a binary mask excluding non-brain voxels was acquired and applied to all volumes. To control for biased reproducibility estimates and false-positive activations, neuronal tissue masking was completed by estimating a probabilistic mask to reduce the variance contribution of non-neuronal tissues in the brain (macro-vasculature, ventricles). This used the PHYCAA+ algorithm (Churchill & Strother, 2013) to estimate task-run and participant-specific neural tissue masks. Nuisance regressors were calculated and concurrently regressed out from the data using general linear model (GLM). A second-order Legendre

polynomial basis set was employed to model temporal trends. Six participant motion parameter estimates obtained from the MOTCOR step were used to model head motion effects. PCA was performed on the motion parameter estimates. The 1-k principal components that accounted for 85% of motion variance were regressed out. Global signal regression was completed by regressing out the first principle component from the fMRI data PCA analysis. Lastly, AFNI's 'SPMG1' hemodynamic response function employing 3dDeconvolve was used to convolve the task paradigm. This regressor and the previously mentioned regressors were included in the GLM.

Employing a two-step registration process using FLS's FLIRT module (Jenkinson et al., 2012) preprocessed fMRI output files were analysed in the same space, aligned to the Montreal Neurological Institute (MNI) template (4 mm resolution). Within participants, the fMRI scan was aligned to the individual's structural T_1-weighted image. Next, the individual's structural image was registered to the MNI template. Transformations from these two steps were combined to align each individual's fMRI scan to the MNI template. FSL's FEAT Version 6.00 was used for first level general linear model (GLM) analysis. Data were high- pass filtered with a cut off of 100 seconds and were FILM prewhitened. Scans with excessive motion were excluded from the analysis based on multivariate outlier detection applied to the motion displacement parameters (see supplemental for more details).

FSL's FEAT was used for higher level GLM analyses. Employing a mixed effects FLAME 1 design, Z (Gaussianised T/F) images were thresholded non-parametrically at $Z > 2.3$ based on the recommendation in Eklund (2016) and a Bonferroni corrected cluster significance threshold.

Demographic and behavioural data analyses were calculated with SPSS 23 (IBM Corporation, 2015). A Holm-Bonferroni correction for multiple comparisons was applied with the exception of behavioural comparisons for the emotional Stroop effect, for which a strong directional hypothesis existed.

Results

Of the 86 MDD and 59 HC participants enrolled in the study, 15 (10%) participants either withdrew from the study or did not attend all study visits. Data lost due to participant study withdrawal were relatively low, compared to other studies (McGrath et al., 2013). Three participants were removed following discovery of incidental findings on structural MRI. As both behavioural and fMRI data were required for at least one run per time point, 49 participants were removed due to missing or corrupted behavioural/fMRI data, or an error level < 30% on more than one run at a time point. With the focus on MDD-8, -16 and -NR, we excluded one patient who was a remitter at 8 weeks and a non-remitter at 16 weeks, as well as four MDD-16 patients who did not receive adjunctive aripiprazole treatment after Week 8, leaving a final N of 30 HC, 16 MDD-8, 12 MDD-16, and 14 MDD-NR. For these 72 participants, 390 of 432 runs (90%)

were included in the analysis (see Table S2). Only baseline and Week 8 data are reported here.

Demographic data are reported in Table 1.

Behavioural Analyses

Between Groups

At baseline there were no significant between group differences between HC and MDD-8, MDD-16, or MDD-NR in RT or accuracy, for *all trials*, or on *congruent* or on *incongruent trials* (see Table S3).

Between groups, at Week 8, MDD-8 were significantly less accurate on the comparison *all trials* (Median = .89) compared to HC (Median = .96), U = 120.5 z = -2.760, p = .006; an effect driven by lower accuracy on *congruent trials* in MDD-8 (Median = .90) compared to HC (Median = .99), U = 123.0 z = -2.738, p = .006 (see Figure 1 and Table S4). There were no significant RT differences between MDD-8 and HC.

There were no Week 8 between-group differences in accuracy or RT between HC and MDD-16 or MDD-NR, or between MDD-8 and MDD-16 (see Table S4).

Within Groups

Within groups at baseline, there was a significant emotional Stroop effect for both accuracy and RT for HC, MDD-8 and MDD-16. MDD-NR demonstrated a significant emotional Stroop effect in RT only (see Figure 1).

Within groups at Week 8, there was a Stroop effect in both accuracy and RT for HC and MDD-8 groups. MDD-16 and MDD-NR groups demonstrated a Stroop effect identified in RT only (see Figure 1).

Comparing baseline and Week 8, there were no changes across time in accuracy or RT within the HC, MDD-8, or MDD-NR groups (see Table S5).

fMRI Analyses

Between Groups

At baseline, lower BOLD activity was observed in MDD-8 compared to HC on comparisons of *all trials* in bilateral brain-stem, thalamus and right caudate, and for *incongruent trials* in bilateral brainstem, and left thalamus (see Table 2). On comparisons of *congruent trials* and *incongruent > congruent trials,* activation patterns for MDD-8 and HC were not significantly different.

Lower baseline BOLD activity was observed for MDD-16 relative to HC on comparisons of *all trials* in right inferior lateral occipital cortex, and temporooccipital part of middle temporal gyrus; on *incongruent trials*, in right inferior lateral occipital cortex, and temporooccipital part of middle temporal gyrus, left occipital pole, superior lateral occipital and cuneal cortex. At baseline, for MDD-16 compared to HC, lower BOLD activity was observed during *incongruent > congruent trials* in bilateral precentral and right postcentral gyri (see Table 2). Comparison of *congruent trials* at baseline between MDD-16 and HC did not identify any significantly different regions of activation.

At baseline, lower BOLD activity was observed in MDD-NR compared to HC in the comparison of *incongruent* > *congruent* trials in bilateral occipital fusiform gyri, precentral gyrus, and cuneal cortex, left lingual gyrus, postcentral gyrus, precuneus and intracalcarine cortex, right insular cortex, putamen, caudate, posterior cingulate gyrus, and posterior and temporooccipital middle temporal gyri (Table 3). Activation patterns for baseline comparisons of *all trials*, *congruent trials*, and *incongruent trials,* between MDD-NR and HC were not significantly different.

At Week 8, between group comparisons of BOLD responses for HC and MDD-8, MDD-16 and MDD-NR, respectively, and between MDD-8 and MDD-16 for *all trials*, *congruent trials*, *incongruent* trials, and *incongruent* > *congruent trials*, were not significantly different.

Within Groups

Within-group comparisons for HC revealed decreased BOLD activity at Week 8, compared to baseline during *congruent trials* in bilateral occipital fusiform gyrus, left temporal occipital fusiform gyrus, right occipital pole, and superior lateral occipital cortex, and on *incongruent trials* in bilateral occipital fusiform gyrus, left lingual gyrus, and right inferior lateral occipital cortex (see Table 4). Comparisons for HC of *all trials* and *incongruent* > *congruent trials,* were not significantly different from baseline to Week 8.

Compared to baseline, MDD-NR demonstrated decreased BOLD activity at Week 8 on *congruent trials* in bilateral lingual gyrus, and occipital pole, left

intracalcarine cortex, and right pre- and post-central gyri. Compared to baseline, MDD-NR demonstrated increased activity at Week 8 on *incongruent > congruent trials* in bilateral lingual gyri, and occipital fusiform gyri, right putamen and insular cortex, and left cerebellar area VI at Week 8 (see Table 5). Comparisons of *all trials* and *incongruent trials* from baseline to Week 8 in MDD-NR were not significant.

Within group comparisons of *all trials*, *congruent trials*, *incongruent trials*, and *incongruent > congruent trials* for MDD-8 and MDD-16, from baseline to Week 8 were not significant.

Discussion

We set out to test the value of an Emotional Conflict Task as a biomarker of subsequent remission or non-remission to escitalopram, or to escitalopram with adjunctive aripiprazole on the basis of behavioural and fMRI BOLD activity indices. All groups demonstrated a robust emotional Stroop effect in RT at both baseline and Week 8. In terms of accuracy, HC, MDD-8 and MDD-16 demonstrated an emotional Stroop effect at baseline, while by Week 8, this effect was only observed in HC and MDD-8. The only between group difference in accuracy at baseline or Week 8 was poorer emotion recognition in MDD-8 compared to HC at Week 8. Baseline BOLD activity was reduced in a number of regions in all MDD groups, compared to HC. However, by Week 8, these differences were no longer observed.

Behavioural

We observed the expected emotional Stroop effect in RT in all groups at baseline and Week 8. At baseline HC, MDD-8 and MDD-16 also demonstrated the emotional Stroop effect in accuracy, while MDD-NR did not, setting it apart from the other groups. By Week 8, HC and MDD-8 continued to show a robust Stroop effect in accuracy, while MDD-16 and MDD-NR did not, possibly due to ceiling effects, and/or as a consequence of the high degree of performance variability within each group.

At baseline, we did not observe significant differences between HC and any of the MDD groups in accuracy or RT on the Emotional Conflict Task. However, at Week 8, accuracy on *congruent trials* was significantly lower in MDD-8 compared to HC, but not on *incongruent trials*, suggesting that the observed between group differences may reflect impaired facial emotion recognition, rather than a decrease in response inhibition. Additionally, as there were no significant differences in RT between MDD-8 and HC at Week 8, lower accuracy in MDD-8 could not be attributed to a speed/accuracy trade-off. Within MDD-8, as mood improves across time, accuracy in emotion recognition decreases. A recent study of the effects of 12 weeks of escitalopram treatment in an elderly MDD sample found improvements in mood occurred more rapidly than changes in cognitive functioning or RT (Beheydt et al., 2015). Another study identified that despite marked improvements in executive function, memory, and attention, following a 24-week trial of escitalopram, MDD patients were still not

functioning as well as a healthy comparison group (Herrera-Guzman et al., 2010). Conversely, MDD-16 did not decrease in emotion recognition accuracy across time, even as mood symptoms improved, suggesting that with the addition of escitalopram treatment, this group processed emotional information differently than MDD-8, even though their mood symptoms did not improve at the same rate as those of MDD-8. Thus, patients in the MDD-16 group may represent a different phenotype of MDD remitter in terms of emotional information processing with escitalopram treatment alone, as well as later positive response to adjunctive treatment with aripiprazole.

fMRI

Neuroimaging findings indicated significantly lower baseline BOLD activity in MDD groups compared to HC, in contrast to our predictions of higher levels of BOLD activity in MDD-8 and lower activity in MDD-NR in rostral cingulate cortex, compared to HC.

In addition, we had predicted higher levels of BOLD activity for MDD-8 in the rostral cingulate cortex, compared to HC. Differences between MDD-8 and HC were limited to lower activity for *all trials* and for the *incongruent* comparison mainly in bilateral brain-stem regions extending to the thalamus and, in the case of the *all trials* comparison, involving also the caudate. The thalamus is involved in visual attention information processing, including diminishing responding to ignored stimuli and increasing responding to attended stimuli (Kastner et al., 2006). The caudate is a component in a circuit important for mood

regulation that comprises the basal ganglia, thalamus, prefrontal cortex, and anterior cingulate cortex (Alexander et al., 1986). Decreased volumes in caudate nucleus, putamen and ACC have been reported in patients with MDD (Bora et al., 2012).

We had predicted lower baseline BOLD activity in MDD-NR in rostral cingulate cortex, compared to HC. We did find lower levels of posterior cingulate activity in MDD-NR compared to HC at baseline, in the *incongruent > congruent trials* comparison, similar to findings of rostral cingulate hypometabolism in MDD treatment non-responders as reported by Mayberg et al., (1997). Additionally, in MDD-NR compared to HC, we observed reduced baseline activity on the *incongruent > congruent* comparison including regions involved in directing attention, such as posterior cingulate cortex, which is important for evaluating valence of emotional words (Maddock et al., 2003) and precuneus, which demonstrates increased activation in response to increased conflict in emotional Stroop tasks (Rahm et al., 2013; Song et al., 2017). Nevertheless, lower activity in these regions in MDD-NR compared to HC did not correspond to a difference in behavioural responding on the Emotional Conflict Task. We also observed reduced baseline activity in MDD-8 compared to HC for *incongruent > congruent* comparison in regions important for facial information processing including: occipital fusiform gyrus, implicated in perception of dynamic and static facial information (Kanwisher et al., 1997; Parvizi et al., 2012), and the lingual gyrus, important in processing facial information (Zhen et al., 2013), reading and

processing lexical stimuli (Borowsky et al., 2007). Both facial perception and lexical processing are necessary processes involved in eliciting the emotional Stroop effect.

Reduced baseline BOLD activity was observed in MDD-16 compared to HC for *all trials* and *incongruent trials* in regions including the right inferior division of the lateral occipital cortex, which is important for emotion recognition and processing of structural aspects of a face (Nagy et al., 2012; Pitcher et al., 2008) and the temporooccipital part of the middle temporal gyrus which is also involved in emotion cognition (Iidaka et al., 2001). Differences in activation patterns between MDD-16 patients and HC for the *incongruent* > *congruent* comparison were restricted to regions of motor and somatosensory cortices. Interestingly, despite lower activity in regions recognized as important for emotion processing, behaviourally, MDD-16 did not perform differently in emotion processing, compared to HC, which suggests that individuals MDD-16 require less engagement of these specific brain regions to perform in this task. Similar to HC, at Week 8, MDD-16 may demonstrate habituation to facial stimuli (Fischer et al., 2003; Spohrs et al., 2018).

Within group differences in HC included reduced activity at Week 8, relative to baseline on *congruent trials* and *incongruent trials* in a number of regions involved in emotion recognition, including bilateral occipital fusiform gyri, and lateral occipital cortex. However, emotional Stroop in HC remained

stable across time, suggesting less neural effort was required by HC to demonstrate emotional Stroop at Week 8.

Baseline neuroimaging indicated lower BOLD activity across all MDD groups compared to HC, which may indicate emotion context insensitivity. Emotion context sensitivity suggests an overall reduced emotional reactivity in MDD, regardless of the context (Bylsma et al., 2008), which may help to explain the apparent blunting in MDD neural responding to stimuli in the Emotional Conflict Task. An overall reduction in engagement with the environment in MDD may occur out of necessity to reduce exposure to negative consequences, diminish the opportunity to make poor choices (Rottenberg, 2005), or to conserve energy (Maes et al., 2012).

While MDD-16 and MDD-NR did not demonstrate mood symptom amelioration to the same degree as MDD-8, in all MDD groups, BOLD activity was altered from baseline to Week 8, so that these groups were no longer significantly different from HC at Week 8. Habituation on an emotion recognition fMRI task has been associated with reduced BOLD activity (Fischer et al., 2003; Spohrs et al., 2018), which HC and MDD-NR demonstrated in a number of regions from baseline to Week 8, without concomitant improvements in RT or accuracy, suggesting BOLD signal augmentation is not necessarily due to a learning effect.

Considering the impaired emotion recognition observed in MDD-8 but not in MDD-16 at Week 8, may be considered within the parameters of the National

Institute of Mental Health's Research Domain Criteria initiative (RDoC). RDoC seeks to incorporate information across neuroscience and genetics to produce a classification system that is trans-diagnostic (Insel et al., 2010). Even though MDD-8, MDD-16 and MDD-NR all belong to the DSM-V category of MDD, their heterogeneous presentation in responding to escitalopram and their different presentations in terms of emotion recognition and mood symptom improvement, suggest different response phenotypes. Differences in emotion recognition may be a sub-domain that ought to be considered across neural disorders in which emotion recognition is known to be impaired, including mood and movement disorders, when adopting a multilateral and domain-specific approach to treatment development and drug discovery (McIntyre, 2014).

One limitation of the Emotional Conflict Task is the lack of a neutral category. It would be interesting to observe whether changes in mood or emotion context insensitivity alter the processing of neutral stimuli. Patients with MDD have more difficulty recognizing ambiguous or neutral facial expressions of emotion (Leppänen et al., 2004), and demonstrate different patterns of neural activity in response to neutral facial expressions (Oliveira et al., 2013), compared to HC. These differences may persist into remission (Leppänen et al., 2004). This is the first study to examine the effects of escitalopram treatment on behavioural responding in an Emotional Conflict Task, and the first study to examine within participant longitudinal performance on this Task. These results indicate that the Emotional Conflict Task is not an objective biomarker for

remission trajectory in patients with MDD receiving escitalopram treatment and escitalopram with adjunctive aripiprazole. Still, we were able to demonstrate that escitalopram ameliorates differences in neural activity between HC and patients with MDD on an fMRI emotional conflict task. The significantly poorer accuracy in MDD-8 compared to HC at Week 8, which was not observed in MDD-16, suggests that improvements in mood in an MDD group receiving escitalopram do not necessarily translate into improvements in emotion recognition. Future work involving a modified Emotional Conflict Task with varying dimensions of emotional valence and the addition of a neutral category may provide richer detail in understanding the nuances of emotion recognition processing in patients experiencing MDD.

Tables and Figures

Table 1. Demographic and clinical information

Variable	HC	MDD-8	MDD-16	MDD-NR	Test
Group *n*	30	16	12	14	--
Female *n* (%)	22 (73%)	12 (75%)	9 (75%)	7 (50%)	X^2 (3) = 3.116, p = 0.374
Right Handed *n* (%)	27 (90%)	16 (100%)	11 (92%)	10 (71%)	X^2 (3) = 9.603, p = 0.142
Age in years	33 ± 10	33 ± 11	34 ± 14	37 ± 13	H(3) = 0.768, p = 0.857
MADRS – Baseline	1 ± 2	27 ± 6	32 ± 5	30 ± 6	H(3) = 55.637, p < 0.0005[#]
MADRS – Week 8	1 ± 2	5 ± 3	21 ± 6	26 ± 10	H(3) = 56.746 , p < 0.0005[##]
MADRS – Week 16	1 ± 1	3 ± 3	5 ± 3	20 ± 7	H(3) = 51.231, p < 0.0005[###]
Length of current MDD Episode in months	--	32 ± 39[X]	24 ± 27[X]	39 ± 35 [X]	H(2) = 2.241, p = 0.326
Number of previous Episodes of MDD	--	4 ± 4[X]	5 ± 4 [XX]	3 ± 4 [X]	H(2) = 1.567, p = 0.457
Level of Education Attained[X] (%)					
8th Grade	-	6%	-	-	X^2 (24) = 31.637, p = 0.136
Grade 11/12 no diploma	-	6%	8%	-	
High School Graduate/GED/Equivalent	20%	6%	17%	29%	
Some college	7%	25%	25%	21%	
Bachelor's or Associate Degree	50%	49%	42%	43%	
Master's /Professional/Doctoral Degree	23%	0%	8%	7%	
Marital Status (%)					
Never Married	60%	50%	58%	36%	X^2 (9) = 8.385, p = 0.496
Separated/Divorced	7%	19%	8%	36%	
Married/Domestic Partnership	30%	25%	25%	29%	
Widowed	3%	6%	8%	-	

Note. Unless otherwise indicated, data are reported as Mean ± SD.
MADRS. Montgomery-Åsberg Depression Rating Scale
[X]Data for one participant missing. [XX]Data for two participants missing
[#]HC < MDD-8, MDD-16, MDD-NR after Bonferroni correction.
[##]HC, MDD-8 < MDD-16, MDD-NR after Bonferroni correction.
[###]HC < MDD-16, MDD-NR; MDD-8 < MDD-NR after Bonferroni correction.

Table 2. Baseline between group comparisons of regional activation on the Emotional Conflict Task in HC versus MDD-8 and MDD-16

Comparison/Anatomical Region	BA	R/L	MNI Coordinates			***p****	**Z -value**	**Cluster Size**
			x	y	z			
All Trials: HC > MDD-8								
Thalamus	-	L	-4	-26	6	0.00078	4.35	730
Brain-stem	-	L	-4	-30	-6		4.19	
Caudate (bilateral)	-	R	8	4	6		3.7	
Brain-stem	-	R	4	-34	-6		3.59	
Brain-stem	-	L	-12	-32	-10		3.26	
Thalamus	-	R	4	0	4		3.21	
Incongruent: HC > MDD-8								
Brain-stem	-	L	-4	-30	-6	0.00382	4.38	586
Brain-stem	-	L	-4	-34	-8		4.12	
Thalamus	-	L	-2	-26	6		3.99	
Brain-stem	-	R	4	-34	-8		3.68	
Brain-stem	-	R	2	-44	-18		3.55	
Brain-stem	-	L	-4	-38	-20		3.49	
All Trials: HC > MDD-16								
Lateral occipital cortex, inferior division	19	R	52	-76	-6	0.00227	3.66	700
Lateral occipital cortex, inferior division	19	R	54	-64	6		3.49	
Lateral occipital cortex, inferior division	-	R	36	-74	10		3.34	
Lateral occipital cortex, inferior division	19	R	40	-78	0		3.31	
Lateral occipital cortex, inferior division	18	R	38	-84	-8		3.00	
Middle temporal gyrus, temporooccipital part	37	R	50	-56	-2		2.96	

Table 2. (Continued)

Comparison/Anatomical Region	BA	R/L	MNI Coordinates			***p****	**Z -value**	**Cluster Size**
			x	y	z			
Incongruent: HC> MDD-16								
Lateral occipital cortex, inferior division	19	R	52	-76	-6	2.15e-06	3.93	1508
Middle temporal gyrus, temporooccipital part	37	R	56	-44	6		3.91	
Lateral occipital cortex, inferior division	37	R	56	-60	2		3.85	
Lateral occipital cortex, inferior division	19	R	54	-64	6		3.74	
Lateral occipital cortex, inferior division	19	R	40	-80	-2		3.47	
Lateral occipital cortex, inferior division	-	R	36	-74	10		3.46	
Cuneal cortex	18	L	-12	-74	28	0.00202	3.64	709
Cuneal cortex	19	L	-18	-78	26		3.22	
Lateral occipital cortex, superior division	7	L	-12	-76	44		3.13	
Lateral occipital cortex, superior division	-	L	-28	-80	8		3.12	
Occipital pole	18	L	-4	-90	24		3.05	
Cuneal cortex	19	L	-10	-84	26		2.97	
Incongruent > Congruent: HC > MDD-16								
Precentral gyrus	-	R	0	-32	64	0.00244	3.26	803
Precentral gyrus	-	R	8	-20	62		3.20	
Precentral gyrus	4	L	-8	-24	68		3.00	
Precentral gyrus	-	L	-12	-32	66		2.92	
Precentral gyrus	6	R	12	-18	72		2.85	
Postcentral gyrus	1	R	16	-36	66		2.84	

BA = Brodmann Area; R/L = Right/Left

* Significant after Bonferroni correction applied

Table 3. Between group comparisons of regional activation on the Emotional Conflict Task in HC versus MDD-NR at baseline

Comparison/ Anatomical Region	BA	R/L	MNI Coordinates			*p**	Z -value	Cluster Size
			x	y	z			
Incongruent > Congruent: HC > MDD-NR								
Occipital fusiform gyrus	19	R	28	-80	-14	1.37e-09	3.52	2997
Occipital fusiform gyrus	-	R	22	-80	-18		3.47	
Occipital fusiform gyrus	18	L	-24	-72	-14		3.4	
Occipital fusiform gyrus	-	L	-28	-76	-18		3.36	
Lingual gyrus	-	L	-8	-68	-6		3.33	
Lingual gyrus	18	L	-12	-76	-8		3.25	
Insular cortex	-	R	36	-4	-6	4.35e-06	3.37	1647
Putamen	49	R	32	0	6		3.23	
Caudate	48	R	12	16	6		3.19	
Putamen	49	R	24	12	-10		3.18	
Putamen	-	R	28	-8	14		3.15	
Putamen	49	R	30	8	-2		3.1	
Precentral gyrus	4	R	20	-28	66	0.000137	3.5	1157
Precentral gyrus	4	R	10	-32	66		3.24	
Postcentral gyrus	7	L	-8	-44	58		3.1	
Postcentral gyrus	5	L	-24	-36	62		3	
Cingulate gyrus, posterior division	-	R	12	-16	38		2.97	
Precentral gyrus	4	L	-24	-24	62		2.97	
Thalamus	-	L	-16	-26	-6	0.000304	3.38	1052
Putamen	49	L	-24	10	4		3.35	
Putamen	49	L	-30	-12	2		3.34	
Putamen	49	L	-24	-2	10		3.26	
Thalamus	-	L	-12	-18	-6		3.26	
Thalamus	50	L	-12	-30	-2		3.12	

Table 3. (Continued)

Comparison/ Anatomical Region	BA	R/L	MNI Coordinates			*p**	Z -value	Cluster Size
			x	y	z			
Incongruent > Congruent: HC > MDD-NR								
Cuneal cortex	19	R	8	-84	36	0.000764	3.27	935
Intracalcarine cortex	17	L	-16	-72	14		3.2	
Precuneus cortex	7	L	8	-76	38		3.09	
Precuneus cortex	19	L	-12	-82	38		3.06	
Cuneal cortex	19	L	-12	-82	32		2.98	
Cuneal cortex	18	L	-8	-88	28		2.86	
Middle temporal gyrus, posterior division	21	R	56	-30	-10	0.00116	3.69	884
Middle temporal gyrus, posterior division	22	R	64	-12	-10		3.18	
Middle temporal gyrus, posterior division	21	R	64	-36	-2		3.16	
Middle temporal gyrus, temporooccipital part	37	R	52	-44	6		3.13	
Middle temporal gyrus, temporooccipital part	37	R	56	-46	-6		3.09	
Middle temporal gyrus, temporooccipital part	37	R	48	-48	8		2.94	

BA = Brodmann Area

*Significant after Bonferroni correction applied

Table 4. Within group comparisons of regional activation on the Emotional Conflict Task in HC at Baseline and Week 8

Comparison/ Anatomical Region	BA	R/L	MNI Coordinates			*p**	Z -value	Cluster Size
			x	y	z			
Congruent: HC Baseline > HC Week 8								
Occipital fusiform gyrus	19	L	-36	-74	-16	0.000307	4.39	703
Occipital fusiform gyrus	19	L	-30	-66	-16		3.62	
Temporal occipital fusiform cortex	-	L	-32	-64	-20		3.61	
Occipital fusiform gyrus	37	L	-40	-66	-20		3.61	
Temporal occipital fusiform cortex	-	L	-40	-62	-24		3.47	
Occipital fusiform gyrus	37	L	-42	-68	-16		3.37	
Occipital fusiform gyrus	19	R	24	-84	-16	0.000436	5.06	674
Occipital pole	18	R	18	-92	8		4.76	
Occipital pole	18	R	20	-92	4		4.53	
Occipital pole	18	R	28	-90	2		3.94	
Lateral occipital cortex, superior division	18	R	38	-88	2		3.71	
Occipital fusiform gyrus	37	R	34	-70	-14		3.63	
Incongruent: HC Baseline > HC Week 8								
Lingual gyrus	18	L	-6	-78	-12	1.79e-07	4.59	1370
Occipital fusiform gyrus	-	L	-38	-74	-20		4.52	
Occipital fusiform gyrus	19	L	-34	-74	-16		4.18	
Occipital fusiform gyrus	-	L	-18	-84	-22		4.04	
Occipital fusiform gyrus	19	L	-30	-66	-16		4.00	
Occipital fusiform gyrus	18	L	-26	-82	-14		3.77	
Occipital fusiform gyrus	19	R	26	-84	-14	1.14e-05	5.21	972
Lateral occipital cortex, inferior division	19	R	42	-70	-16		4.42	
Occipital fusiform gyrus	19	R	22	-84	-16		4.21	
Occipital fusiform gyrus	37	R	38	-70	-20		4.18	
Occipital fusiform gyrus	-	R	32	-72	-20		4.00	
Lateral occipital cortex, inferior division	-	R	38	-74	-22		3.94	

BA = Brodmann Area

*Significant after Bonferroni correction applied

Table 5. Within group comparisons of regional activation on the Emotional Conflict Task in MDD-NR at Baseline and Week 8

Comparison/ Anatomical Region	BA	R/L	MNI Coordinates			*p**	Z - value	Cluster Size
			x	y	z			
Congruent: MDD-NR Baseline > MDD-NR Week 8								
Lingual gyrus	18	R	10	-88	-6	2.6e-16	4.17	3201
Intracalcarine cortex	17	L	-14	-88	6		4.13	
Occipital pole	18	L	-24	-92	14		4.00	
Occipital pole	18	R	8	-88	12		3.8	
Lingual gyrus	18	L	-16	-80	-4		3.66	
Occipital pole	18	R	8	-88	16		3.59	
Postcentral gyrus	4	R	36	-20	42	0.000469	3.58	544
Postcentral gyrus	1	R	44	-32	60		3.22	
Postcentral gyrus	1	R	42	-24	52		3.15	
Precentral gyrus	6	R	24	-16	70		3.07	
Postcentral gyrus	1	R	56	-20	38		3.06	
Precentral gyrus	4	R	38	-24	54		2.93	
Incongruent > Congruent: MDD-NR Baseline < MDD-NR Week 8								
Lingual gyrus	18	L	-16	-78	-2	0.00119	3.04	621
Lingual gyrus	18	L	-12	-74	-4		2.94	
Lingual gyrus	18	L	-8	-80	-6		2.94	
Cerebellar area VI	-	L	-8	-72	-12		2.92	
Lingual gyrus	-	L	-12	-76	-14		2.92	
Occipital fusiform gyrus	18	L	-20	-72	-8		2.88	
Insular cortex	-	R	36	0	6	0.00178	3.04	588
Putamen	49	R	28	4	-2		3.02	
Putamen	-	R	32	-16	-6		2.97	
Putamen	49	R	28	-4	6		2.92	
Putamen	49	R	32	-4	2		2.91	
Putamen	49	R	32	-8	4		2.91	
Lingual gyrus	19	R	16	-48	-6	0.00262	3.25	557
Lingual gyrus	19	R	12	-64	2		3.09	
Occipital fusiform gyrus	-	R	30	-80	-18		3.07	
Lingual gyrus	19	R	16	-68	-10		3.06	
Lingual gyrus	18	R	12	-72	2		3.03	
Lingual gyrus	18	R	12	-68	-2		2.94	

BA = Brodmann Area

*Significant after Bonferroni correction applied

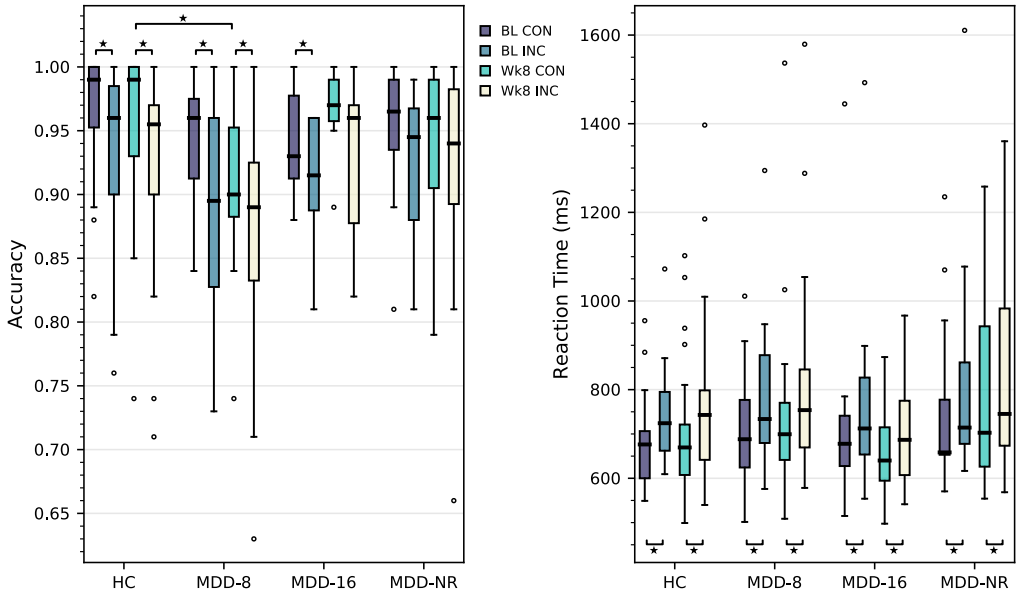

Figure 1. Emotional Conflict Task Accuracy and Reaction Time (RT) Results The box-plots show medians as thick horizontal lines, while boxes represent the interquartile range (IQR), and whiskers extend beyond the boxes by 1.5×IQR. Stars (★) indicate significant differences at $p < 0.05$, after correction for multiple comparisons where appropriate. Reaction time data exhibited a significant emotional Stroop effect in all groups at all time-points, while an emotional Stroop effect was not significant in accuracy for the MDD-16 group at Week 8 or in the MDD-NR group at either time point. **BL**: data from baseline visit; **Wk8**: data collected 8 weeks after treatment initiation; **CON/INC**: congruent/incongruent stimulus condition.

Supplementary Material

Table S1. Scanning protocol deviations

Site	Scanning Protocol Deviation
One GE Discovery site	Scanned without parallel imaging acceleration
Philips site	Scanned with a 1 mm inter-slice gap
	Used a flip angle of 90º
Siemens site	Used TE = 25 ms

Table S2. Reasons for runs being excluded from final Emotional Conflict Task analysis, by grouping, and run number.

	GROUPING												
	CONTROL						MDD						
	Baseline		Week 2		Week 8		Baseline		Week 2		Week 8		
	RUN		RUN		RUN		RUN		RUN		RUN		
Exclusion Criteria	1	2	1	2	1	2	1	2	1	2	1	2	Total (%)
Total Runs	55	55	55	55	55	55	71	71	71	71	71	71	756 (100%)
Missing/corrupted behavioural data	8	7	2	2	2	3	1	-	2	-	1	1	29 (4%)
Missing/corrupted/poor quality fMRI data	12	15	11	11	13	15	13	23	14	19	15	18	179 (24%)
Too many errors in behavioural data	3	1	1	1	3	5	5	5	2	6	9	7	48 (6%)
Total Runs Lost	23	23	14	14	18	23	19	28	18	25	25	26	256 (33%)

Note: Data for participants that withdrew/missed a visit or had incidental findings on the structural MRI are not included.

Table S3. Emotional Conflict Task – Baseline between group comparisons

Baseline Comparison	**HC**	**MDD-8**	***Test***
Accuracy All Trials	.97	.92	$U = 143.5$ $z = -2.230$, $p = 0.026$, $r = .33$
Accuracy Congruent Trials	.99	.96	$U = 158.5$ $z = -1.914$, $p = 0.056$, $r = .28$
Accuracy Incongruent Trials	.96	.90	$U = 142.0$ $z = -2.263$, $p = 0.024$, $r = .33$
RT All Trials	705 ms	711 ms	$U = 288$ $z = 1.107$, $p = 0.268$, $r = .16$
RT Congruent Trials	676 ms	688 ms	$U = 276$ $z = 0.830$, $p = 0.406$, $r = .12$
RT Incongruent Trials	724 ms	733 ms	$U = 282$ $z = 0.969$, $p = 0.333$, $r = .14$
	HC	**MDD-16**	
Accuracy All Trials	.96	.92	$U = 112.0$ $z = -1.90$, $p = 0.060$, $r = .29$
Accuracy Congruent Trials	.99	.93	$U = 114.5$ $z = -1.877$, $p = 0.068$, $r = .29$
Accuracy Incongruent Trials	.96	.92	$U = 115.5$ $z = -1.799$, $p = 0.072$, $r = .28$
RT All Trials	705 ms	693 ms	$U = 197.0$ $z = 0.473$, $p = 0.650$, $r = .07$
RT Congruent Trials	676 ms	678 ms	$U = 196.0$ $z = 0.445$, $p = 0.670$, $r = .07$
RT Incongruent Trials	724 ms	712 ms	$U = 186.0$ $z = 0.167$, $p = 0.880$, $r = .03$
	HC	**MDD-NR**	
Accuracy All Trials	.97	.94	$U = 155.0$ $z = -1.390$, $p = 0.165$, $r = .21$
Accuracy Congruent Trials	.99	.97	$U = 156.0$ $z = 1.390$, $p = 0.165$, $r = .21$
Accuracy Incongruent Trials	.96	.95	$U = 168.5$ $z = -1.047$, $p = 0.295$, $r = .16$
RT All Trials	705 ms	688 ms	$U = 233.0$ $z = 0.580$, $p = 0.562$, $r = .09$
RT Congruent Trials	676 ms	658 ms	$U = 248.0$ $z = 0.958$, $p = 0.338$, $r = .14$
RT Incongruent Trials	724 ms	714 ms	$U = 225.0$ $z = 0.378$, $p = 0.705$, $r = .06$

Note: Data are reported as Medians. *Significant at $p \leq .05$ after Holm-Bonferroni correction.

Table S4. Emotional Conflict Task – Week 8 between group comparisons

Comparison	HC	MDD-8	Test
Accuracy All Trials	.96	.89	$U = 120.5$ $z = -2.760$, $p = 0.006$*, $r = .41$
Accuracy Congruent Trials	.99	.90	$U = 123.0$ $z = -2.738$, $p = 0.006$*, $r = .40$
Accuracy Incongruent Trials	.95	.89	$U = 136.5$ $z = -2.389$, $p = 0.017$, $r = .35$
RT All Trials	705 ms	726 ms	$U = 269.0$ $z = 0.669$, $p = 0.504$, $r = .10$
RT Congruent Trials	670 ms	699 ms	$U = 284.0$ $z = 1.015$, $p = 0.310$, $r = .15$
RT Incongruent Trials	743 ms	754 ms	$U = 261.0$ $z = 0.484$, $p = 0.628$, $r = .07$
	HC	**MDD-16**	
Accuracy All Trials	.96	.97	$U = 174.0$ $z = -0.168$, $p = 0.880$, $r = .03$
Accuracy Congruent Trials	.99	.97	$U = 159.0$ $z = -0.594$, $p = 0.573$, $r = .09$
Accuracy Incongruent Trials	.95	.96	$U = 174.0$ $z = -0.167$, $p = 0.880$, $r = .26$
RT All Trials	705 ms	673 ms	$U = 144.0$ $z = -1.02$, $p = 0.328$, $r = .16$
RT Congruent Trials	670 ms	640 ms	$U = 153.0$ $z = -0.752$, $p = 0.466$, $r = .12$
RT Incongruent Trials	743 ms	687 ms	$U = 143.0$ $z = -1.03$, $p = 0.314$, $r = .16$

Table S4. (continued)

Comparison	HC	MDD-NR	Test
Accuracy All Trials	.96	.96	$U = 194.5$ $z = -0.392$, $p = 0.695$, $r = .06$
Accuracy Congruent Trials	.99	.96	$U = 169.5$ $z = -1.042$, $p = 0.297$, $r = .16$
Accuracy Incongruent Trials	.95	.94	$U = 203.5$ $z = -0.164$, $p = 0.870$, $r = .02$
RT All Trials	705 ms	721 ms	$U = 237.0$ $z = 0.680$, $p = 0.496$, $r = .10$
RT Congruent Trials	670 ms	703 ms	$U = 258.0$ $z = 1.21$, $p = 0.226$, $r = .18$
RT Incongruent Trials	743 ms	745 ms	$U = 220.0$ $z = 0.252$, $p = 0.801$, $r = .04$
	MDD-8	**MDD-16**	
Accuracy All Trials	.89	.97	$U = 145.5$ $z = 2.303$, $p = 0.020$, $r = .42$
Accuracy Congruent Trials	.90	.97	$U = 151.0$ $z = 2.557$, $p = 0.010$, $r = .47$
Accuracy Incongruent Trials	.89	.96	$U = 135.5$ $z = 1.835$, $p = 0.066$, $r = .34$
RT All Trials	726 ms	673 ms	$U = 72.0$ $z = -1.114$, $p = 0.280$, $r = .20$
RT Congruent Trials	699 ms	640 ms	$U = 69.0$ $z = -1.253$, $p = 0.223$, $r = .23$
RT Incongruent Trials	753 ms	687 ms	$U = 72.0$ $z = -1.114$, $p = 0.280$, $r = .20$

Note: Data are reported as Medians. *Significant at $p \leq .05$ after Holm-Bonferroni correction.

Table S5. Emotional Conflict Task – Baseline and Week 8 within group comparisons

Comparison	Baseline	Week 8	Test
		HC	
Accuracy All Trials	.97	.96	$z = -0.927$, $p = 0.354$, $r = .12$
Accuracy Congruent Trials	.99	.99	$z = -0.640$, $p = 0.523$, $r = .08$
Accuracy Incongruent Trials	.96	.96	$z = -0.789$, $p = 0.430$, $r = .10$
RT All Trials	705 ms	705 ms	$z = 0.000$, $p = 1.00$, $r = .00$
RT Congruent Trials	676 ms	670 ms	$z = 0.183$, $p = 0.855$, $r = .02$
RT Incongruent Trials	724 ms	743 ms	$z = -0.183$, $p = 0.855$, $r = .02$
		MDD-8	
Accuracy All Trials	.92	.89	$z = -1.592$, $p = 0.111$, $r = .28$
Accuracy Congruent Trials	.96	.90	$z = -2.066$, $p = 0.035$, $r = .37$
Accuracy Incongruent Trials	.90	.89	$z = -1.250$, $p = 0.210$, $r = .22$
RT All Trials	711 ms	726 ms	$z = 0.750$, $p = 0.454$, $r = .13$
RT Congruent Trials	688 ms	699 ms	$z = 1.250$, $p = 0.210$, $r = .22$
RT Incongruent Trials	733 ms	754 ms	$z = -0.750$, $p = 0.454$, $r = .13$

Table S5. (continued)

Comparison	Baseline	Week 8	Test
MDD-16			
Accuracy All Trials	.92	.97	$z = 2.00, p = 0.039, r = .41$
Accuracy Congruent Trials	.93	.97	$z = 1.206, p = 0.227, r = .25$
Accuracy Incongruent Trials	.92	.96	$z = 2.021, p = 0.039, r = .41$
RT All Trials	693 ms	673 ms	$z = -0.866, p = 0.388, r = .18$
RT Congruent Trials	678 ms	640 ms	$z = -0.866, p = 0.388, r = .18$
RT Incongruent Trials	712 ms	687 ms	$z = -1.443, p = 0.146, r = .29$
MDD-NR			
Accuracy All Trials	.94	.96	$z = 0.000, p = 1.000, r = .00$
Accuracy Congruent Trials	.97	.96	$z = -0.734, p = 0.463, r = .14$
Accuracy Incongruent Trials	.95	.94	$z = 0.000, p = 1.000, r = .00$
RT All Trials	688 ms	721 ms	$z = -0.267, p = 0.791, r = .05$
RT Congruent Trials	658 ms	703 ms	$z = -0.267, p = 0.791, r = .05$
RT Incongruent Trials	714 ms	745 ms	$z = -0.802, p = 0.424, r = .15$

Note: Data are reported as Medians.

Supplementary Methods

Multivariate Outlier Detection

To detect scans corrupted by motion, the average of each of the six rigid-body motion parameter estimates was calculated for each time-series. Three multivariate outlier detection techniques were then applied to the six mean motion parameters from each site. The outlier detection methods included: 1) a FAST-MCD (minimum covariance determinant) [203]; 2) a bootstrap version of MCD using "component score" distance; and 3) a bootstrap version of MCD using Mahalanobis distance. These algorithms flagged any scans whose mean motion was away from the distribution mean in any direction. Thus, participants could also be flagged when having minimal motion compared to the rest of the scans from a particular site. To address this, results of outlier detection techniques were combined with a *total-displacement* (TD) value calculated based on the 6 motion parameters for each scan:

$$TD = \sqrt{(d_x + 75r)^2 + \left(d_y + 75y\right)^2 + (d_z + 75p)^2}$$

Where d_X, d_Y and d_Z are displacements on the right-left, anterior-posterior and interior-superior axes respectively, and roll (r), yaw (y) and pitch (p), with values in radians, respectively.

The decision to remove a particular scan from further analysis was based on the following criteria: 1) a scan was flagged by at least two outlier detection methods and TD of the scan was ≥ 1 SD of the mean TD for all sites, or, 2) a scan was

flagged by one outlier detection method and TD of the scan was > 2 SD of the mean TD for the entire sample.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci,* 9, 357-381. doi:10.1146/annurev.ne.09.030186.002041

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: Author.

Beheydt, L. L., Schrijvers, D., Docx, L., Bouckaert, F., Hulstijn, W., & Sabbe, B. (2015). Cognitive and psychomotor effects of three months of escitalopram treatment in elderly patients with Major Depressive Disorder. *J Affect Disord,* 188, 47-52. doi:10.1016/j.jad.2015.08.041

Blair, R. J. R. (2003). Facial expressions, their communicatory functions and neuro-cognitive substrates. *Philos Trans R Soc Lond B Biol Sci,* 358(1431), 561-572. doi:10.1098/rstb.2002.1220

Bora, E., Harrison, B. J., Davey, C. G., Yucel, M., & Pantelis, C. (2012). Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in Major Depressive Disorder. *Psychol Med,* 42(4), 671-681. doi:10.1017/S0033291711001668

Borowsky, R., Esopenko, C., Cummine, J., & Sarty, G. E. (2007). Neural representations of visual words and objects: a functional MRI study on the modularity of reading and object processing. *Brain Topogr,* 20(2), 89-96. doi:10.1007/s10548-007-0034-1

Bouhuys, A. L., Geerts, E., & Gordijn, M. C. (1999). Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. *J Nerv Ment Dis,* 187(10), 595-602. doi:10.1097/00005053-199910000-00002

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in Major Depression: a review. *Aust N Z J Psychiatry,* 44, 681-696. doi:10.3109/00048674.2010.496359

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in Major Depressive Disorder. *Clin Psychol Rev,* 28(4), 676-691. doi:10.1016/j.cpr.2007.10.001

Campbell, K. L., Grigg, O., Saverino, C., Churchill, N., & Grady, C. L. (2013). Age differences in the intrinsic functional connectivity of default network subsystems. *Front Aging Neurosci,* 5, 1-12. doi:10.3389/fnagi.2013.00073

Carton, J. S., Kessler, E. A., & Paper, C. L. (1999). Nonverbal decoding skills and relatiohship well-being in adults. *J Nonverbal Beh,* 23(1), 91-100. doi:10.1023/A:1021339410262

Churchill, N. W., Spring, R., Afshin-Pour, B., Dong, F., & Strother, S. C. (2015). An automated, adaptive framework for optimizing preprocessing pipelines in task-based functional MRI. *PLoS One,* 10(7), e0131520. doi:10.1371/journal.pone.0131520

Churchill, N. W., & Strother, S. C. (2013). PHYCAA+: an optimized, adaptive procedure for measuring and controlling physiological noise in BOLD fMRI. *Neuroimage,* 82, 306-325. doi:10.1016/j.neuroimage.2013.05.102

Cox, R. W. (1996). AFNI: software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Comput Biomed Res,* 29, 162-173. doi:10.1006/cbmr.1996.0014

Dalili, M. N., Penton-Voak, I. S., Harmer, C. J., & Munafò, M. R. (2015). Meta-analysis of emotion recognition deficits in Major Depressive Disorder. *Psychol Med*, 1135-1144. doi:10.1017/S0033291714002591

Darwin, C. (1872). *The expression of the emotions in man and animals*. London, UK: John Murray.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *PNAS,* 113(28), 7900-7905. doi:10.1073/pnas.1602413113

Ekman, P., & Friesen, W. V. (1976). Pictures of Facial Affect: Consulting Psychologists Press.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron,* 51(6), 871-882. doi:10.1016/j.neuron.2006.07.029

Etkin, A., & Schatzberg, A. F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in Generalized Anxiety and Major Depressive Disorders. *Am J Psychiatry,* 168(9), 968-978. doi:10.1176/appi.ajp.2011.10091290

Favre, P., Polosan, M., Pichat, C., Bougerol, T., & Baciu, M. (2015). Cerebral correlates of abnormal emotion conflict processing in euthymic bipolar

patients: a functional MRI study. *PLoS One,* 10(8), e0134961-0134916. doi:10.1371/journal.pone.0134961

Fischer, H., Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2003). Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull,* 59(5), 387-392. doi:10.1016/s0361-9230(02)00940-1

Fournier, J., Chase, H., Greenberg, T., Etkin, A., Almeida, J., Stiffler, R., . . . Phillips, M. (2017). Neuroticism and individual differences in neural function in unmedicated Major Depression: findings from the EMBARC study. *Biol Psychiatry Cogn Neurosci Neuroimaging,* 2(2), 138-148. doi:10.1016/j.bpsc

Frey, B. N., Hall, G. B., Attard, S., Yucel, K., Skelin, I., Steiner, M., & Soares, C. N. (2010). Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point? *Menopause,* 17(4), 840-845. doi:10.1097/gme.0b013e3181df840f

Friedman, L., Glover, G. H., Krenz, D., & Magnotta, V. (2006). Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. *Neuroimage,* 32(4), 1656-1668. doi:10.1016/j.neuroimage.2006.03.062

Gotlib, I. H., Jonides, J., Buschkuehl, M., & Joormann, J. (2011). Memory for affectively valenced and neutral stimuli in depression: evidence from a novel matching task. *Cogn Emot,* 25(7), 1246-1254. doi:10.1080/02699931.2010.538374

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol,* 6, 285-312. doi:10.1146/annurev.clinpsy.121208.131305

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci,* 368(1615), 20120407. doi:10.1098/rstb.2012.0407

Hawley, C. J., Gale, T. M., & Sivakumaran, T. (2002). Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disord,* 72(2), 177-184. doi:10.1016/S0165-0327(01)00451-7

Herrera-Guzman, I., Herrera-Abarca, J. E., Gudayol-Ferre, E., Herrera-Guzman, D., Gomez-Carbajal, L., Pena-Olvira, M., . . . Joan, G. O. (2010). Effects of selective serotonin reuptake and dual serotonergic-noradrenergic

reuptake treatments on attention and executive functions in patients with Major Depressive Disorder. *Psychiatry Res,* 177(3), 323-329. doi:10.1016/j.psychres.2010.03.006

Hill, A. B., & Knowles, T. H. (1991). Depression and the 'emotional' Stroop effect. *Person Individ Diff,* 12(5), 481-485. doi:10.1016/0191-8869(91)90066-K

IBM Corporation. (2015). IBM SPSS Statistics for Macintosh, Version 23.0 (Version 23.0). Armonk, NY, USA: IBM Corporation.

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., & Sadato, N. (2001). Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *J Cogn Neurosci,* 13(8), 1035-1047. doi:10.1162/089892901753294338

Imbault, C., & Kuperman, V. (2018). Emotional reactivity and perspective-taking in individuals with and without severe depressive symptoms. *Sci Rep,* 8(1), 7634. doi:10.1038/s41598-018-25708-x

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Doman Criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry,* 167(7), 748-751. doi:10.1176/appi.ajp.2010.09091379

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

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci,* 17(11), 4302-4311. doi:10.1523/JNEUROSCI.17-11-04302.1997

Kastner, S., Schneider, K. A., & Wunderlich, K. (2006). Beyond a relay nucleus: neuroimaging views on the human LGN. *Prog Brain Res,* 155, 125-143. doi:10.1016/s0079-6123(06)55008-3

Kennedy, S. (2002). Full remission: a return to normal functioning. *J Psychiatry Neurosci,* 27(4), 233-234. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12174731

Kennedy, S. H., Lam, R. W., Rotzinger, S., Milev, R. V., Blier, P., Downar, J., . . . on behalf of the CAN-BIND Investigator Team. (2019). Symptomatic and functional outcomes and early prediction of response to escitalopram monotherapy and sequential adjunctive aripiprazole therapy in patients with Major Depressive Disorder. *J Clin Psychiatry,* 80(2), e1-e10. doi:10.4088/JCP.18m12202

Kudlow, P. A., Cha, D. S., & McIntyre, R. S. (2012). Predicting treatment response in Major Depressive Disorder: the impact of early symptomatic improvement. *Can J Psychiatry,* 57(12), 782-788. doi:10.1177/070674371205701211

Lam, R. W., Milev, R., Rotzinger, S., Andreazza, A. C., Blier, P., Brenner, C., . . . and on behalf of the CAN-BIND Investigator Team. (2016). Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. *BMC Psychiatry,* 16(1), 105. doi:10.1186/s12888-016-0785-x

Leppänen, J., Milders, M., Bell, J. S., Terriere, E., & Hietanen, J. K. (2004). Depression biases the recognition of emotionally neutral faces. *Psychiatry Res,* 128(2), 123-133. doi:10.1016/j.psychres.2004.05.020

MacQueen, G. M., Hassel, S., Arnott, S. R., Jean, A., Bowie, C. R., Bray, S. L., . . . on behalf of the CAN-BIND Investigator Team. (2019). The Canadian Biomarker Integration Network in Depression (CAN-BIND): magnetic resonance imaging protocols. *J Psychiatry Neurosci,* 44(3), 1-14. doi:10.1503/jpn.180036

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp,* 18(1), 30-41. doi:10.1002/hbm.10075

Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Galecki, P., & Leonard, B. (2012). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med,* 10, 66. doi:10.1186/1741-7015-10-66

Mayberg, H. S., Brannan, S. K., Mahurin, R. K., Jerabek, P. A., Brickman, J. S., Tekell, J. L., . . . Fox, P. T. (1997). Cingulate function in depression: a potential predictor of treatment response. *NeuroReport,* 8(4), 1057-1061. doi:10.1097/00001756-199703030-00048

McGrath, C. L., Kelley, M. E., Holtzheimer, P. E., Dunlop, B. W., Craighead, W. E., Franco, A. R., . . . Mayberg, H. S. (2013). Toward a neuroimaging treatment selection biomarker for Major Depressive Disorder. *JAMA Psychiatry,* 70(8), 821-829. doi:10.1001/jamapsychiatry.2013.143

McIntyre, R. S. (2014). A vision for drug discovery and development: novel targets and multilateral partnerships. *Adv Ther,* 31(3), 245-246. doi:10.1007/s12325-014-0105-0

Mendlewicz, J. (2008). Towards achieving remission in the treatment of depression. *Dialogues Clin Neurosci,* 10(4), 371-375. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19170394

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *Brit J Psychiat,* 134, 382-389. doi:10.1192/bjp.134.4.382

Nagy, K., Greenlee, M. W., & Kovacs, G. (2012). The lateral occipital cortex in the face perception network: an effective connectivity study. *Front Psychol,* 3, 141. doi:10.3389/fpsyg.2012.00141

Oliveira, L., Ladouceur, C. D., Phillips, M. L., Brammer, M., & Mourao-Miranda, J. (2013). What does brain response to neutral faces tell us about Major Depression? Evidence from machine learning and fMRI. *PLoS One,* 8(4), e60121. doi:10.1371/journal.pone.0060121

Parvizi, J., Jacques, C., Foster, B. L., Witthoft, N., Rangarajan, V., Weiner, K. S., & Grill-Spector, K. (2012). Electrical stimulation of human fusiform face-selective regions distorts face perception. *J Neurosci,* 32(43), 14915-14920. doi:10.1523/JNEUROSCI.2609-12.2012

Paykel, E. S. (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues Clin Neurosci,* 10(4), 431-437. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19170400

Paykel, E. S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychol Med,* 25(6), 1171-1180. doi:10.1017/S0033291700033146

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J Neurosci,* 28(36), 8929-8933. doi:10.1523/JNEUROSCI.1450-08.2008

Rahm, C., Liberg, B., Wiberg-Kristoffersen, M., Aspelin, P., & Msghina, M. (2013). Rostro-caudal and dorso-ventral gradients in medial and lateral prefrontal cortex during cognitive control of affective and cognitive interference. *Scand J Psychol,* 54(2), 66-71. doi:10.1111/sjop.12023

Rey, G., Desseilles, M., Favre, S., Dayer, A., Piguet, C., Aubry, J.-M., & Vuilleumier, P. (2014). Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: preliminary findings from a follow-up state-based fMRI study. *Psychiatry Res,* 223(2), 84-93. doi:10.1016/j.pscychresns.2014.04.016

Romera, I., Perez, V., Menchon, J. M., Delgado-Cohen, H., Polavieja, P., & Gilaberte, I. (2010). Social and occupational functioning impairment in patients in partial versus complete remission of a Major Depressive Disorder episode. A six-month prospective epidemiological study. *Eur Psychiatry,* 25(1), 58-65. doi:10.1016/j.eurpsy.2009.02.007

Rottenberg, J. (2005). Mood and emotion in Major Depression. *Curr Dir Psychol Sci,* 14(3), 167-170. doi:10.1111/j.0963-7214.2005.00354.x

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in Major Depressive Disorder. *J Abnorm Psychol,* 114(4), 627-639. doi:10.1037/0021-843X.114.4.627

Rousseeuw, P. J., & Van Driessen, K. (1999). A fast algorithm for the minimum covariance determinant estimator. *Technometrics,* 41(3), 212-223. doi:10.1080/00401706.1999.10485670

Rubinow, D. R., & Post, R. M. (1992). Impaired recognition of affect in facial expression in depressed patients. *Biol Psychiatry,* 31(9), 947-953. doi:10.1016/0006-3223(92)90120-O

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-Prime User's Guide* (2.0 ed.). Pittsburgh: Psychology Software Tools, Inc.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry,* 59 Suppl 20, 22-57. doi:10.1016/S0924-9338(97)83296-8

Song, S., Zilverstand, A., Song, H., d'Oleire Uquillas, F., Wang, Y., Xie, C., . . . Zou, Z. (2017). The influence of emotional interference on cognitive

control: a meta-analysis of neuroimaging studies using the emotional Stroop task. *Sci Rep,* 7(1), 2088. doi:10.1038/s41598-017-02266-2

Spohrs, J., Bosch, J. E., Dommes, L., Beschoner, P., Stingl, J. C., Geiser, F., . . . Viviani, R. (2018). Repeated fMRI in measuring the activation of the amygdala without habituation when viewing faces displaying negative emotions. *PLoS One,* 13(6), e0198244. doi:10.1371/journal.pone.0198244

Strother, S. C. (2006). Evaluating fMRI preprocessing pipelines. *IEEE Eng Med Biol Mag,* 25(2), 27-41. doi:10.1109/MEMB.2006.1607667

Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in Major Depression: a systematic review of neuroimaging findings. *Biol Mood Anxiety Disord,* 1(1), 10. doi:10.1186/2045-5380-1-10

Taylor, B. P., Bruder, G. E., Stewart, J. W., McGrath, P. J., Halperin, J., Ehrlichman, H., & Quitkin, F. M. (2006). Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. *Am J Psychiatry,* 163(1), 73-78. doi:10.1176/appi.ajp.163.1.73

Torres-Quesada, M., Korb, F. M., Funes, M. J., Lupiáñez, J., & Egner, T. (2014). Comparing neural substrates of emotional vs. non-emotional conflict modulation by global control context. *Front Hum Neurosci,* 8, 1-14. doi:10.3389/fnhum.2014.00066

Vanderhasselt, M. A., De Raedt, R., Dillon, D. G., Dutra, S. J., Brooks, N., & Pizzagalli, D. A. (2012). Decreased cognitive control in response to negative information in patients with remitted depression: an event-related potential study. *J Psychiatry Neurosci,* 37(4), 250-258. doi:10.1503/jpn.110089

World Health Organization. (2008). *The Global Burden of Disease 2004 Update* Geneva: World Health Organization.

Xue, S., Wang, S., Kong, X., & Qiu, J. (2017). Abnormal neural basis of emotional conflict control in treatment-resistant depression: an event-related potential study. *Clin EEG Neurosci,* 48(2), 103-110. doi:10.1177/1550059416631658

Zhen, Z., Fang, H., & Liu, J. (2013). The hierarchical brain network for face recognition. *PLoS One,* 8(3), e59886. doi:10.1371/journal.pone.0059886

Chapter 6

Volumetric MRI analysis of a case of severe ventriculomegaly

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Abstract

We present a case of a 60-year-old male referred to a tertiary psychiatric facility for diagnostic assessment due to low mood and behavioral changes. Neurological examination of the patient was unremarkable. Magnetic resonance imaging (MRI) indicated overt ventriculomegaly with gross dilatation of lateral and third ventricles. Manual segmentation of gray matter, white matter and cerebrospinal fluid demonstrated that the patient had a ventricular volume almost 46 times greater than that of healthy volunteers in the same age range. Despite his striking degree of ventriculomegaly and cortical thinning, he presented primarily with psychiatric and cognitive complaints. These represented a major neurocognitive disorder. His behavior improved with a structured environment and routine instituted by the treating team. This is a dramatic example of the brain's response to extreme structural remodeling. Elements of pluripotentiality may counteract degeneracy to preserve functions in cases of serious structural stress in the brain. Changes in the neural circuitry of emotional processing, and/or disruption in signaling pathways important for synaptogenesis may influence depression pathophysiology. How this circuitry is modified in cases of extreme structural stress such as long-standing overt ventriculomegaly, is unclear. This case demonstrates the ability of the brain to generate a normal phenotype despite structural changes that seem incompatible with advanced cognitive function, illustrating the substantial potential for adaptability and plasticity in the brain.

Key Words: ventriculomegaly, hydrocephalus, depression, ventricles, MRI, segmentation, neuroplasticity.

Introduction

The idea of applying brain imaging to explore psychiatric disorders is not new (Andreasen, 1988); nonetheless, psychiatry has not yet found many clinical roles for neuroimaging. One of the challenges has been that although we can obtain detailed imaging of brain structure with a resolution of 0.8-1 mm, anatomical abnormalities are not specific, and it is often difficult to correlate them with brain function. Extreme cases of hydrocephalus that demonstrate this principle have been described in the literature (Canu et al., 2005; Feuillet et al., 2007; Lewin, 1980). Indeed, long-standing overt ventriculomegaly in adults has been proposed as a unique clinical entity, comprised of a form of chronic hydrocephalus that progresses without the clinical and behavioral symptoms that would be expected, given the often quite dramatic degree ventricular enlargement (Oi et al., 1996; Oi et al., 2000). The clinical manifestations of hydrocephalus depend on the time of appearance and nature of onset (Del Bigio, 2010). While some data gathered from rats and humans have suggested that the degree of ventricular dilatation may be associated with the degree of motor and cognitive deficits (Del Bigio et al., 2003; Olopade et al., 2012), this is not always the case (de Oliveira et al., 2011). Dr. John Lorber famously described a student with an IQ of 126 and an honors degree in mathematics, who was socially normal despite having massive hydrocephalus and only a thin mantle of cortical thickness (Lewin, 1980). Another described case is that of a 44-year-old married father of two who worked as a civil servant (Feuillet et al., 2007). Despite having severe hydrocephalus, he had an IQ of 75,

verbal IQ of 84, and lived a relatively normal life; although, he did suffer from leg weakness, which had prompted his presentation. In the context of psychiatric disorders, it is important to identify any underlying organic causes.

Here we present the case of a 60-year-old male who presented with mood symptoms and was referred to a tertiary psychiatric facility for diagnostic clarification and treatment recommendations for depressed mood. Interestingly, despite his striking degree of ventriculomegaly and cortical matter loss, he presented with few neurological findings and presented with primarily psychiatric and cognitive complaints.

A written consent from the patient substitute decision maker was obtained, providing consent for the publication of this report.

Case Presentation

Patient CS, a single 60-year-old male presenting with a history of generalized anxiety with panic, major depressive disorder, and excessive guilt, was referred from a county hospital to a tertiary psychiatric facility for clarification of diagnosis and a more comprehensive assessment. His sister, and the family physician that had been following the patient for the past four years, helped provide collateral history. His family noted that he was born with a large head. He had a history of meningitis at the age of 9 or 10 after which it is thought that he developed a non-communicating hydrocephalus. His past psychiatric diagnoses included major depressive disorder, generalized anxiety disorder with panic, personality disorder, and “borderline intelligence”. He had several admissions to a

psychiatric ward over the past 3 years for low mood and had been trialed on numerous psychotropic medications (citalopram, lithium carbonate, risperidone, olanzapine, quetiapine, paliperidone, clomipramine, clonazepam, lorazepam) with little effect or benefit. At the time of admission, he did not smoke, drink alcohol, or take illicit drugs. His past medical history was significant for hypothyroidism corrected with the use of thyroxine, bowel resections secondary to possible malignant changes, fatty liver with lobar resection secondary to liver cancer, and nephrolithiasis.

He was born and raised in Europe until the age of 5, when he immigrated to Canada, and is bilingual. His family reported that he had always had a large head, micropenis, central obesity and short stature. He had a history of being bullied for "looking like a girl" and being different. At school his peers were physically aggressive, hitting him on his head. Born the youngest of 7 siblings, he was raised by his parents and lived under their care into adulthood, until both parents passed away – his father had Diabetes Miletus and his mother had a brain tumor. Thereafter, he was taken care of by his sister. He had an older brother who also passed away secondary to a brain malignancy. One brother has dyslipidemia, and two sisters and one brother are healthy. He had no employment history and as a child had always struggled in school, completing a vocational stream of education until grade 10. Socially, he was active in a band for a few years (plays guitar well) and sang in a church choir. However, he never lived independently, and had no romantic relationships.

Initial assessment revealed that he was a poor historian unable to give an accurate timeline of events. He often expressed fears that he was going to die. He suffered from delusions of guilt that he had caused the deaths of family members. His conversation was repetitive, he repeatedly asked the same questions and restated his fear of dying despite several reassurances. He had no history of self-harm or suicide attempts. On physical examination, he had a wide stance waddling gait, slow movements, limited arm swing and masked facies. He was noted to have enlarged head circumference (62.5 cm) and limited insight into his illness and the need for treatment. His clinical presentation prompted examination with magnetic resonance imagining (MRI) of the brain and formal neuropsychological testing.

Investigations

Magnetic Resonance Imaging

A sagittal T1, axial T2, axial T2 FLAIR, and diffusion-weighted images were acquired throughout the brain. Findings indicated a long-standing overt ventriculomegaly, likely due to aqueductal stenosis, with bilateral gross dilation of the lateral and third ventricles, with a small aqueduct and fourth ventricle, with significant thinning of the corpus callosum and overlying cerebral cortex. Vascular flow-voids at the base of the brain were normal and there were no mass lesions, significant sulcal effacement, downward tonsillar herniation or restricted diffusion observed.

Manual segmentation of grey and white matter, and cerebrospinal fluid (Figure 1) of high-resolution T1 weighted MRI images was completed with Freeviewer in FSL (Jenkinson et al., 2012). Automatic segmentation of sex and age matched healthy controls (one aged 60, three aged 55 years, Table 1) was completed with the FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) recon tool. The participant's volumes were converted to Z scores for comparison. Compared to similarly aged control participants, the patient had extremely large ventricular volume (821,452 mm^3, Z = 161), reduced white (333,606 mm^3, Z = -2.655) and grey (432,184 mm^3, Z = -3.07) matter volume, and within normal range total intracranial volume (1,587,242 mm^3, Z = 0.57) see Table 1 and Figure 1.

Neurological Assessment

The patient's neurological exam was unremarkable

Neuropsychological Assessment

The Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) revealed a borderline IQ of 79, with a verbal IQ of 88, non-verbal performance IQ of 74, poor working memory IQ of 71, verbal comprehension IQ of 93, and visual-spatial IQ of 80. The patient had difficulty completing tasks requiring working memory, which was in the 3rd percentile, and processing speed was extremely slow (in the 1st percentile). Hopkins Auditory Verbal Learning Test (Brandt, 1991) indicated severe memory impairment, with initial memory for only a few items, no significant recall between administrations, and inability to recall any information after a brief delay. Rey-Osterrieth Complex Figure Task (Osterrieth,

1944; Rey et al., 2014) performance indicated impaired visual spatial and working memory abilities with more attention to small details, missing elements, and less attention to the overall image. The Stroop test (Stroop, 1935) indicated impaired executive function, scoring below the 1st percentile, with a severe inability to suppress automatic responses.

Treatment

Patient CS was referred for a neurosurgery consult due to what appeared to be a long-standing history of hydrocephalus. The neurosurgery service recommended no role for neurosurgical intervention as there had been no recent decompensation of his chronic hydrocephalus. It was concluded that the patient's increasing inability to cope at home and worsening cognitive ability represented an early onset major neurocognitive disorder. Interestingly, he may have suffered from panhypopituitarism that is known to be a rare exclusive presentation of chronic hydrocephalus (Edwards et al., 2004). Nonetheless, his sensory and motor deficits were noncontributory to his presentation compared to his mood and cognitive complaints.

While on the inpatient ward, his behavior improved due to having a structured environment and routine instituted by the treating team. In particular, he responded well to positive reinforcement and encouragement that reinforced positive behaviors, such as playing his guitar (including a 3-hour jam session) and socializing with those around him. Furthermore, his rumination regarding guilt that he had somehow caused the death of his loved ones decreased when he was

repeatedly given a rational explanation for their deaths. Treatment involved tapering the patient off most of his psychotropic medications. At discharge, the patient continued only on his thyroxine and cholestyramine as well as a small dose of citalopram due to patient's and family's preference, and their hopes that this would help reduce his anxiety symptoms.

Discussion

This case provides a dramatic example of the brain's adaptability in response to extreme structural remodeling and demonstrates one extreme of the clinical manifestations of long-standing hydrocephalus. What seems clear is that the brain has mechanisms in place for reorganization and preservation of function, such as redundancy or spared capacity (Lewin, 1980). This allows adaptability and functional reorganization of neural circuits, resulting in the retention of function. While the patient had ventricles almost 46 times greater than similar aged individuals, his grey and white matter volume, although appearing 'compressed', was, to a large extent, preserved. He was dependent, with some preserved functioning, no neurological complaints, presenting primarily with psychiatric and cognitive complaints. This may be influenced by structural relationships of pluripotentiality of the human brain (a one-to many structure-function relationship) (Friston & Price, 2003), which may come at the cost of utilizing the cerebral reserve (Canu et al., 2005), and may be a reasonable explanation for his early onset of cognitive difficulties and perhaps a disposition (heightened vulnerability) for mood disturbances.

A recent review provides evidence for topographically organized interconnected networks between cerebellum, basal ganglia, and the cortex, that span processing of cognitive, motor, and affective information (Bostan & Strick, 2018). This may be a network level example of degeneracy (Friston & Price, 2003) – "the ability of elements that are structurally different to perform the same function or yield the same output"(Edelman & Gally, 2001) and may explain some of the patient's preserved function, including being fluent in two languages and mastering playing a musical instrument. Altered cortical mapping in congenitally blind humans suggests cortical regions are 'cognitively pluripotent' during neurodevelopment, with regions associated with vision changing developmental trajectory to process information from different sensory modalities, shaped by experience and limited by physical connectivity (Bedny, 2017). Elements of pluripotentiality may counteract degeneracy to preserve functions in such cases of serious structural remodeling in the brain.

When we conceptualize psychiatric disorders, we believe that they originate in the brain and result from a complex interaction of genetic and environmental factors. However, understanding how psychiatric illness develops and manifests itself within the brain has proven to be far from a simple task. Convergent data from post-mortem studies and neuroimaging suggest that abnormalities in the neural circuitry underlying emotional processing play an important role in the pathophysiology of depression (Price & Drevets, 2010). Individuals who experience severe or prolonged stress are at an increased risk for

neuropathological effects of stress including development of depression and other psychiatric disorders (Lucassen et al., 2014). Social and environmental risk factors, and adverse experiences, modulated by genetic factors, have been shown to impact the same neural circuits that underlie mood regulation (Meyer-Lindenberg & Tost, 2012). Further, disruption of principle signaling pathways important for synaptogenesis are associated with the pathophysiology of depression (Duman et al., 2016). While the precise mechanism of action of antidepressant treatments remains unclear, it has been suggested that they may work by enhancing neuronal plasticity (Castrén & Hen, 2013), providing one explanation for the delay between when treatment is initiated and when patients begin to experience symptom amelioration (Harmer & Cowen, 2013). It is through visualizing psychiatric disorders as disorders in neural circuitry that novel treatments like deep brain stimulation have been and continue to be developed (Lozano & Lipsman, 2013). Less invasive psychological and pharmacological interventions utilizing this model have yet to be developed. As this case demonstrates, the ability of the brain to generate a normal phenotype despite structural changes that seem incompatible with advanced cognitive function, illustrate the potential for adaptability and plasticity within the brain.

Tables and Figures

Table 1. Comparison of ventricular volume, white matter, grey matter, and total estimated intracranial volume in patient CS compared to sex and age matched controls

Participant (Age)	Ventricular Volume* (mm^3) %	White Matter Volume** (mm^3) %	Grey Matter Volume*** (mm^3) %	Total Estimated Intracranial Volume mm^3
HC1 (60)	(18,642) 1.31%	(409,828) 29%	(563,787) 40%	1,419,546
HC2 (55)	(12,917) 0.91%	(418,055) 29%	(550,945) 39%	1,420,196
HC3 (55)	(24,599) 1.49%	(489,911) 30%	(670,738) 41%	1,648,324
HC4 (55)	(15,786) 0.99%	(492,760) 31%	(613,109) 39%	1,590,823
Means	(17,986) 1.18%	(452,639) 30%	(599,645) 39%	1,519,722
Patient CS	(821,452) 51.75%	(333,606) 21%	(432,184) 27%	1,587,242[#]
Patient CS Z scores	161.0	-2.655	-3.07	0.57

* Left and right lateral ventricles, left and right inferior lateral ventricles, third and fourth ventricles

** Left and right hemisphere cortical white matter

*** Subcortical grey matter, left and right hemisphere cortex, cerebellar grey matter

[#] Total intracranial volume mm^3

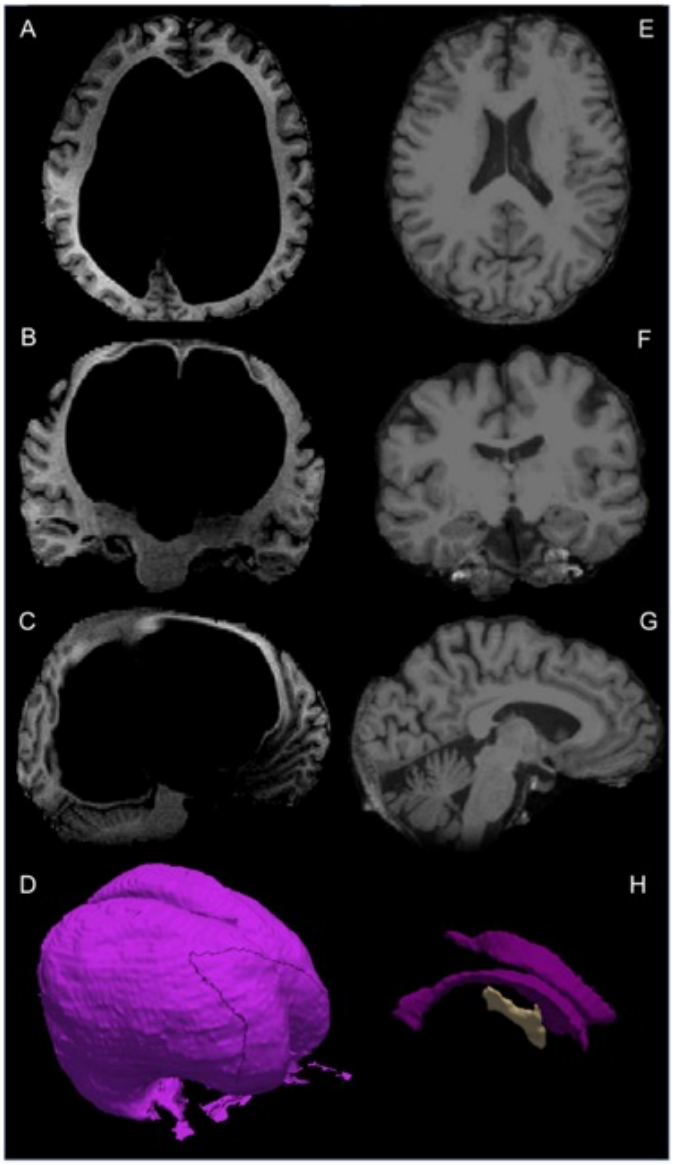

Figure 1. From top to bottom: T1-weighted magnetic resonance imaging (MRI) images in the transverse, coronal, and sagittal planes of Patient CS (A-C) and a healthy age- and sex-matched control participant healthy control 1 (HC1) aged 60 (E-G). Three dimensional image of Patient CS' ventricular space (D), and (H) three dimensional images of left and right lateral, and third ventricles taken from the Freesurfer (Dale et al., 1999) average of 35 brains template.

References

Andreasen, N. C. (1988). Brain imaging: applications in psychiatry. *Science,* 239(4846), 1381-1388. doi:10.1126/science.3279509

Bedny, M. (2017). Evidence from blindness for a cognitively pluripotent cortex. *Trends Cogn Sci,* 21(9), 637-648. doi:10.1016/j.tics.2017.06.003

Bostan, A. C., & Strick, P. L. (2018). The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci,* 19(6), 338-350. doi:10.1038/s41583-018-0002-7

Brandt, J. (1991). The Hopkins verbal learning test: development of a new memory test with six equivalent forms. *Clin Neuropsychol,* 5(2), 125-142. doi:10.1080/13854049108403297

Canu, E. D. G., Magnano, I., Paulus, K. S., Piras, M. R., Conti, M., Costantino, S., . . . Aiello, I. (2005). Neuropsychophysiological findings in a case of long-standing overt ventriculomegaly (LOVA). *Neuroscience Letters,* 385(1), 24-29. doi:10.1016/j.neulet.2005.05.026

Castrén, E., & Hen, R. (2013). Neuronal plasticity and antidepressant actions. *Trends Neuroscie,* 36(5), 259-267. doi:10.1016/j.tins.2012.12.010

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage,* 9(2), 179-194. doi:10.1006/nimg.1998.0395

de Oliveira, M. F., Pinto, F. C., Nishikuni, K., Botelho, R. V., Lima, A. M., & Rotta, J. M. (2011). Revisiting hydrocephalus as a model to study brain resilience. *Front Hum Neurosci,* 5, 181. doi:10.3389/fnhum.2011.00181

Del Bigio, M. R. (2010). Neuropathology and structural changes in hydrocephalus. *Dev Disabil Res Rev,* 16(1), 16-22. doi:10.1002/ddrr.94

Del Bigio, M. R., Wilson, M. J., & Enno, T. (2003). Chronic hydrocephalus in rats and humans: white matter loss and behavior changes. *Ann Neurol,* 53(3), 337-346. doi:10.1002/ana.10453

Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med,* 22(3), 238-249. doi:10.1038/nm.4050

Edelman, G. M., & Gally, J. A. (2001). Degeneracy and complexity in biological systems. *Proc Natl Acad Sci USA,* 98(24), 13763-13768. doi:10.1073/pnas.231499798

Edwards, R. J., Dombrowski, S. M., Luciano, M. G., & Pople, I. K. (2004). Chronic hydrocephalus in adults. *Brain Pathology,* 14(3), 325-336. doi:10.1111/j.1750-3639.2004.tb00072.x

Feuillet, L., Dufour, H., & Pelletier, J. (2007). Brain of a white-collar worker. *Lancet,* 370(9583), 262. doi:10.1016/S0140-6736(07)61127-1

Friston, K. J., & Price, C. J. (2003). Degeneracy and redundancy in cognitive anatomy. *Trends Cogn Sci,* 7(4), 151-152. doi:10.1016/S1364-6613(03)00054-8

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci,* 368(1615), 20120407. doi:10.1098/rstb.2012.0407

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

Lewin, R. (1980). Is your brain really necessary? *Science,* 210(4475), 1232-1234. doi:10.1126/science.7434023

Lozano, A. M., & Lipsman, N. (2013). Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron,* 77(3), 406-424. doi:10.1016/j.neuron.2013.01.020

Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F., Van Dam, A. M., Rajkowska, G., . . . Czeh, B. (2014). Neuropathology of stress. *Acta Neuropathol,* 127(1), 109-135. doi:10.1007/s00401-013-1223-5

Meyer-Lindenberg, A., & Tost, H. (2012). Neural mechanisms of social risk for psychiatric disorders. *Nat Neurosci,* 15(5), 663-668. doi:10.1038/nn.3083

Oi, S., Sato, O., & Matsumoto, S. (1996). Neurological and medico-social problems of spina bifida patients in adolescence and adulthood. *Child's Nervous System: ChNS: official journal of the International Society for Pediatric Neurosurgery,* 12(4), 181-187. doi:10.1007/BF00301248

Oi, S., Shimoda, M., Shibata, M., Honda, Y., Togo, K., Shinoda, M., . . . Sato, O. (2000). Pathophysiology of long-standing overt ventriculomegaly in adults. *J Neurosurg,* 92(6), 933-940. doi:10.3171/jns.2000.92.6.0933

Olopade, F. E., Shokunbi, M. T., & Sirén, A.-L. (2012). The relationship between ventricular dilatation, neuropathological and neurobehavioural changes in hydrocephalic rats. *Fluids Barriers CNS,* 9(19), 1-10. doi:10.1186/2045-8118-9-19

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives of Psychology,* 30, 206-356.

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology,* 35(1), 192-216. doi:10.1038/npp.2009.104

Rey, G., Desseilles, M., Favre, S., Dayer, A., Piguet, C., Aubry, J.-M., & Vuilleumier, P. (2014). Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: preliminary findings from a follow-up state-based fMRI study. *Psychiatry Res,* 223(2), 84-93. doi:10.1016/j.pscychresns.2014.04.016

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J Exp Psychol,* 18, 643-662. doi:10.1037/h0054651

Wechsler, D. (1997). *WAIS-III administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Chapter 7

General Discussion

The brain has the capacity to modify to adapt to novel circumstances (Demarin et al., 2014). Some changes in neural circuitry may begin as adaptive measures in response to stress such as hypervigilance in response to a threat situation (McEwen et al., 2012). If this behavior and the concomitant neural changes in circuitry persist once the peril passes, it becomes maladaptive and could facilitate changes leading to the development of psychiatric disorders such as major depressive disorder (MDD) (Liu et al., 2017; McEwen et al., 2012). Advances in neuroimaging technology have facilitated the study of neuroplastic changes in the brain in patients with MDD. While the pathogenesis of MDD is still unclear, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may be involved in the etiology of MDD (Menke, 2019) and of MDD in perimenopause (Gordon et al., 2015) and may promote the neuroplastic changes observed in MDD (Belleau et al., 2019; Dillon & Pizzagalli, 2018; McEwen, 1999; Pittenger & Duman, 2008). Whether neuroplastic changes precede MDD or occur as a result of MDD is still unclear (Schmaal et al., 2015). The hippocampus is a stress sensitive structure and recent advances in automated tissue segmentation have suggested that greater hippocampal volume reductions are associated with increased disease duration (Roddy et al., 2019), but have been observed as well in MDD patients in

a first presentation of MDD (Roddy et al., 2019). However, a large meta-analysis found no differences between healthy control participants, and patients experiencing a first major depressive episode (MDE) (Schmaal et al., 2015). Characterizing functional similarities and differences between patients with MDD and healthy comparison participants (HC) is key to establishing the baseline level of neural functioning in patients, prior to treatment begin. Being able to characterize how neural functional activity changes across time as a result of treatment with antidepressants may provide valuable information in the quest to identify a biomarker to predict antidepressant response in MDD. There are still gaps in understanding the degree, timing, and extent of neuroplastic changes in depression, and how they are affected by antidepressant treatment. The research presented in this dissertation aims to provide additional characterization and context to neuroplastic changes that accompany depression.

Chapter 2 presented the data from a study examining hippocampal function and cognitive performance in treatment naïve patients presenting for treatment for MDD for the first time, on a hippocampal-dependent memory task. The study objective was to assess whether differences in cognitive and functional neuroimaging measures of hippocampal activity can be observed in treatment naïve patients presenting for treatment for MDD for the first time, given that changes in hippocampal integrity have been associated with MDD. Study results indicated that on behavioural measures of guessing, recollection memory and habit memory, the MDD patient group did not differ from HC as has been

previously reported (Bazin et al., 1994; MacQueen et al., 2002). These results may be contrasted with results of a process dissociation task in a sample of mostly unmedicated MDD patients with a first MDE, MDD patients with multiple MDEs and HC, in which both patient groups demonstrated impaired recollection memory compared to HC, but not compared to each other, and MDD groups' performances were similar to HC in terms of habit memory and guessing (MacQueen et al., 2003). Findings from a study of MDD patients with at least 3 MDE reported that patients were impaired on both recollection and habit memory compared to HC (Milne et al., 2012). The findings in our study must be interpreted cautiously, as it is possible that a sample of patients presenting for the first time, even though not necessarily experiencing a first MDE, may have common characteristics that contribute to the similar performance on the process dissociation task between MDD and HC. With respect to fMRI findings in Chapter 2, functional neuroimaging data indicated that the MDD group demonstrated increased neural activity in bilateral hippocampus on habit memory trials and increased bilateral activity in parahippocampal gyrus on non-item trials, without demonstrating a corresponding impairment in hippocampus-dependent memory, as compared to the comparison group. While increased activity in bilateral hippocampal gyrus on recollection memory trials was observed in MDD compared to the comparison group, these results were not significant after correction for multiple comparisons. However, taken together, these results suggest that to perform similarly to the comparison group on a process

dissociation memory task, patients in the MDD group (who were acutely depressed at the time of the study) needed to recruit more neural resources, suggesting that even at a first presentation for MDD treatment, differences in hippocampal functioning were already present. These results suggest that the increased neural activity observed in the MDD group, with no significant differences between groups in behavioural measures, may be implemented as a compensatory mechanism. These findings may be compared with observations of memory performance in patients with MDD receiving antidepressant treatment including dysregulation in hippocampal function on a memory task (no relationship between hippocampal neural activity and memory task performance) and the recruitment of an additional region – intraparietal sulcus, in spite of no differences in behavioural performance (Fairhall et al., 2010); an inability to regulate hippocampal neural activation on an associative spatial memory task on which an MDD group with extensive MDD history performed poorly compared to HC (Finkelmeyer et al., 2016); and a reduction in neural activity in hippocampal and parahippocampal gyri on a process dissociation task in patients with extensive history of MDD with poorer performance on both habit and recollection memory trials compared to healthy control participants (Milne et al., 2012). These findings also suggest that in this sample of patients, habit and recollection memory in a process dissociation task are not discernably influenced by mood. This is similar to the findings of MacQueen et al. (2002), who report that patients with more MDEs had a greater likelihood for impaired recollection memory, and that

patients responding to antidepressant treatment did not perform significantly better than patients that did not respond to antidepressant treatment, on a process-dissociation memory task. MacQueen et al. (2002) concluded that past burden of illness may have a greater influence on memory abilities than current mood state, as having a lower depression symptom score did not translate into better recollection memory scores. The persistence of cognitive impairment in MDD when patients reach a euthymic state suggests a dissociation of cognitive impairment and mood symptoms (Zuckerman et al., 2018).

As antidepressant treatment may alter hippocampal functioning (Wessa & Lois, 2015) and structure (Dusi et al., 2015; Frodl et al., 2008), a particular strength of the study was that we were able to apply an fMRI process dissociation task that specifically measured hippocampus-dependent memory in an antidepressant treatment naïve sample of patients with MDD presenting for treatment for the first time. This allowed us to observe functional differences in hippocampal functioning prior to the application of an antidepressant treatment, which may change functional activity patterns in hippocampus (Wessa & Lois, 2015) as well as hippocampal morphology (Dusi et al., 2015; Frodl et al., 2008). Use of an ROI approach allowed us to make a more direct connection between brain structure and function and neutralize the effects of anatomical inter-subject variability without spatially smoothing data, which contributes to the blurring of regional boundaries and can decrease statistical test sensitivity and greatly

decrease resolution (mindhive: A community portal for MIT brain research, 2008; Nieto-Castanon et al., 2003).

In terms of limitations, although our sample was antidepressant treatment naïve and presenting for treatment for MDD for the first time, participants were not necessarily experiencing a first MDE (mean of 2.6 MDE). It is possible that results may have differed examining hippocampus-dependent memory in a group of patients experiencing a first MDE, as opposed to experiencing the most recent of several MDEs, given that progressive neuroplastic changes in the hippocampus appears to be occurring in patients that experience recurrent episodes of MDD (Roddy et al., 2019; Schmaal et al., 2015). In addition to this, our ROI approach concentrating exclusively on the hippocampus meant that we were unable to verify whether additional bran regions were recruited when completing the process dissociation task. A related limitation is that while the approach of manually tracing the ROI on a summed co-registered anatomical image at the group level allows for the disambiguation of amygdala from the anterior hippocampal region (Boccardi et al., 2011; Yucel et al., 2008), we cannot rule out that the traced ROIs may have included activity contributed by voxels in the amygdala due to partial volume effects (Dukart & Bertolino, 2014). Finally, the sample size was modest (N = 13 HC, 13 MDD). A larger sample size may have increased the power of our study.

In spite of these limitations, this study provided evidence that there is different hippocampal function with preserved memory function in an MDD

treatment naïve group compared to HC. This suggests that changes in hippocampal functional activity may be present early in MDD development, possibly prior to the emergence of changes in hippocampal morphometry. Building on these findings, a repeated measures longitudinal study of functional activation during hippocampus-dependent memory tasks together with an examination of changes in integrity of hippocampal substructures and concomitant changes in MDD symptomatology would provide greater insight and context to the progressive changes that occur in hippocampus in patients with MDD.

Chapter 3 presented data from a study examining the differential effects of an acute tryptophan depletion (ATD) paradigm on emotional Stroop performance in a sample of midlife women receiving estrogen-based treatment. The study objective was to examine the modulatory effect of estrogen treatment (ET) on mood through the interaction of estrogen on the serotonergic system in perimenopausal women receiving ET. While there was a significant reduction in mood and vasomotor symptoms in the study sample after beginning ET, ATD did not elicit significant changes in mood or vasomotor symptoms, suggesting that mediation of the effects of ET on thermoregulation and mood may not be facilitated via immediate availability of serotonin. Alternately, it is possible that the high dose of transdermal ET administered to participants compensated for reductions in serotonergic availability effected through ATD, providing a state of serotonergic homeostasis, and thus avoiding the emergence of mood deterioration

that may accompany ATD. In terms of the emotional Stroop task, there were no differences between ATD and Sham conditions in behavioural responses as measured by reaction time (RT) and accuracy scores. The emotional Stroop effect was evident within both conditions as measured by RT, similar to previously published studies in HC groups (Etkin et al., 2006; Frey et al., 2010; Wortinger et al., 2017) and in a group of perimenopausal to late menopausal women not receiving ET (Frey et al., 2010). The expected effect of higher accuracy on congruent compared to incongruent trials was not detected (Etkin et al., 2006; Gold et al., 2015; Wortinger et al., 2017), and is also similar to previous findings in a group of perimenopausal to late menopausal women not receiving ET (Frey et al., 2010). A key difference in behavioural results between conditions was that incongruent adaptation (the tendency to respond faster and more accurately on an incongruent trial preceded by an incongruent trial compared to an incongruent trial preceded by a congruent trial) was observed in the Sham condition in accuracy but not RT, which is supported by previous findings (Chechko et al., 2014; Clayson & Larson, 2013; Gold et al., 2015; Krug & Carter, 2010). On the contrary, in the ATD condition incongruent adaptation was observed only in RT, while no difference in accuracy was observed, similar to previous findings in a group of perimenopausal to late menopausal women not receiving ET (Frey et al., 2010). In terms of neuroimaging, the study found lower levels of neural activity in ATD compared to Sham for incongruent adaptation in lateral occipital cortex, angular gyrus, caudate, and middle temporal gyrus. The caudate is involved in

emotion regulation (Alexander et al., 1986), while middle temporal gyrus is important for emotion processing (Iidaka et al., 2001). Observing incongruent adaptation in RT and the reversal in the expected response facilitation in ATD, together with reduced neural activity in regions important for processing of emotional information suggests that serotonin availability may be important for the processing of conflicting emotional information. Conversely, increased neural activity in ATD compared to Sham on the emotional Stroop comparison and on incongruent trials and on cI trials without accompanying differences in behavioural performance, suggests that supplementary neural regions may be recruited to attain levels of responding similar to those observed in the Sham condition.

A strength of using ATD is that this manipulation allowed us to examine the effect of low serotonin levels on processing of emotional information without the confound of low mood. This was also the first study to observe the effects of ATD on behavioural and functional neural activity on emotional Stroop in a group of midlife women receiving transdermal ET.

In terms of limitations, this study would have been strengthened with the inclusion of baseline Sham and ATD testing of participants prior to starting ET, or the inclusion of a two group of participants with high and low levels of mood symptoms prior to starting ET. This would have enabled us to measure changes in emotion facilitated by addition of ET, and to determine whether temporary depletion of tryptophan levels prior to ET begin would have had measurable

effects on behavioural and functional responding on an Emotional Conflict Task in women at different risk levels for developing perimenopausal MDD. A further limitation is the modest sample size, which limits the generalizability of our results.

Notwithstanding these limitations, this study was important in that it was the first to report effects of ATD on behavioural and functional neural activity on emotional Stroop in a group of midlife women receiving transdermal ET. The findings support the hypothesis that the influence of transdermal ET on mood in perimenopause may be mediated by its influence on longer lasting changes in the serotonergic system including increased serotonin receptor density (Moses-Kolko, 2003; Rybaczyk et al., 2005) and serotonin efficacy (Rybaczyk et al., 2005), which are less likely to be influenced by an acute reduction in serotonin availability as is the case in ATD.

Chapter 4 presented findings from a study comparing performance of unmedicated patients with MDD and HC on a series of cognitive tasks including RT, cognitive flexibility, executive functioning and simple Stroop RT as measured by the CNS-Vital Signs (CNS-VS; Gualtieri & Johnson, 2006) computerized test battery, and on an fMRI Emotional Conflict Task. The study objective was to characterize baseline differences between an unmedicated MDD group as a whole and HC on an Emotional Conflict Task, as part of a larger study of longitudinal data from this group which, due to the volume of information, was divided and the second part is presented in Chapter 5. This study found that RT,

as measured by scores on a computerized test battery, was not significantly different between MDD and HC groups. This research identified that unmedicated patients with MDD and HC both showed a strong emotional Stroop effect as measured by RT and accuracy, which is similar to previously reports (Chechko et al., 2009; Cheng et al., 2015; Etkin et al., 2006; Etkin & Schatzberg, 2011; Fournier et al., 2017; Wortinger et al., 2017). Nevertheless, the MDD group showed overall lower accuracy scores compared to HC, in contrast to other studies comparing MDD and HC (Etkin et al., 2006; Fournier et al., 2017). HC demonstrated incongruent adaptation in RT, but not accuracy, which has also been noted in other studies (Chechko et al., 2009; Etkin et al., 2006). However, MDD demonstrated incongruent adaptation in accuracy but not RT, which is also a result that has been previously reported in HC (Clayson & Larson, 2013; Krug & Carter, 2010). Gold et al. (2015) suggest two types of incongruent adaptation involving (a) response facilitation which would be measured by RT and (b) skill in execution of the task, which would be measured by accuracy. In terms of the current study, the unmedicated MDD group demonstrated incongruent adaptation in task execution, without experiencing a facilitation in RT. Neuroimaging findings indicated that MDD demonstrated lower neural activity on a number of comparisons in the core neural network important for face perception, including lateral occipital cortex, which is involved in emotion recognition and in processing structural aspects of the face (Nagy et al., 2012; Pitcher et al., 2008), the superior temporal sulcus, which is involved in identification of dynamic facial

features (Puce et al., 1998), and occipital fusiform gyrus, which facilitates perception of dynamic and static facial information (Kanwisher et al., 1997; Parvizi et al., 2012). Decreased neural activity in regions associated with emotional conflict resolution and perception of faces may be related to the overall reduced levels of accuracy identified in the MDD group. Although the lower levels of neural activity were observed in the MDD group in anterior supramarginal gyrus (associated with automatic reading (Stoeckel et al., 2009)), and left planum temporale (associated with silent reading of single words (Buchsbaum et al., 2005)), the MDD group still demonstrated a robust Stroop effect. Further, a number of neural regions in which lower levels of neural activity were observed in MDD compared to HC belong to the ACC-basal ganglia-thalamocortical circuit, or the 'limbic' circuit (Alexander et al., 1986). The most prominent finding of this study was the overall decrease in task-related neural activity compared to HC, in addition to the findings that there were no between group differences in behavioural or neural activity in fear > happy trials. Contrary to some prevailing theories of emotional information processing in MDD (Bhagwagar et al., 2004; Scheele et al., 2013), this suggests that this sample of patients with MDD did not interpret emotional information through the lens of a negative bias. Instead, the overall reduction in accuracy suggests a generalized insensitivity to emotion, regardless of valence, as previously reported (Persad & Polivy, 1993). However, other studies have reported no between group differences in neural activity (Fournier et al., 2017), or recruitment of additional neural

regions when completing the Emotional Conflict Task (Etkin & Schatzberg, 2011). Conflicting findings such as these, may be considered within the schema of the National Institute of Mental Health's Research Domain Criteria initiative (RDoC), which encourages empirical data integration across genetic and neuroscience platforms to promote a cross-diagnostic classification rubric (Insel et al., 2010). As outlined in the introduction, MDD symptomatology can vary from patient to patient, including symptoms that span both extremes of a spectrum (insomnia to hypersomnia, psychomotor slowing to agitation, significant weight loss to significant weight gain). Grouping participants by symptom or emotional information processing style, rather than altogether under the umbrella of a single diagnosis, may bring characteristics of these groups into sharper relief, and help to reduce and explain the large range of variance observed in studies examining emotional information processing in MDD, including the current study. It is entirely possible that a sub-type of participant with MDD may adhere to a negative attention bias or have trouble disengaging from negative information (Bouhuys et al., 1999; Bourke et al., 2010; Gotlib et al., 2011; Stuhrmann et al., 2011), while patients in a different sub-group may display behaviour that conforms more closely to the emotion context insensitivity hypothesis – the idea of an overall reduction in responding to emotional stimuli, regardless of the valence (Bylsma et al., 2008; Rottenberg, 2005).

A limitation to this study is the criticism that the Emotional Conflict Task addresses only “hot” cognition due to a focus on emotional stimuli (Roiser &

Sahakian, 2013) and a lack of neutral or ambiguously valenced stimuli. From the perspective of Becks' cognitive model of depression (Beck, 2002), MDD patients may either project 'heat' from their own negative cognitions and expectations onto neutral or ambiguous stimuli or these cognitions may influence the bottom-up processing of stimuli with emotional valence (Roiser & Sahakian, 2013). However, it is likely that elements of emotion and cognition are integrated and contribute to response selection rather than operating independently (Pessoa, 2008). Nevertheless, a future study may benefit from the inclusion of a neutral category in the Emotional Conflict Task.

Although this study had some limitations, these results provided evidence of reduced accuracy and reduced neural activity in an unmedicated sample of patients with MDD compared to HC, with a preserved emotional Stroop in terms of RT and accuracy. A key finding was the lack of between group differences in processing of happy versus fearful faces, and in the MDD group specifically, the overall lower accuracy in emotion recognition, and overall reduction in neural activity across several contrasts related to Stroop execution, compared to HC. The lack of between group differences in processing of happy versus fearful faces contests the negative attention bias hypothesis (Bhagwagar et al., 2004; Scheele et al., 2013), and provides support for the emotion context insensitivity hypothesis (Rottenberg et al., 2005) which posits that in MDD there is an overall blunting of responding to emotional stimuli regardless of the valence, as observed in our study. The emotion context insensitivity hypothesis explains decreased emotional

reactivity in MDD as an overall hesitation to initiate motivated action in response to external emotional cues (Rottenberg et al., 2005) and we observed decreased neural activity in MDD compared to HC on the Emotional Conflict Task.

Chapter 5 presented the results of a study examining the baseline predictive value of indices of task-based behavioural and neural activity on an Emotional Conflict task in determining remission or non-remission in response to treatment with escitalopram or escitalopram with adjunctive aripiprazole in unmedicated patients with MDD and HC. MDD patients were divided into groups of patients who reached remission week 8 post-treatment begin (MDD-8), at week 16 post-treatment begin (MDD-16), or who did not reach remission at either week 8 or 16 (MDD-NR). A strong emotional Stroop effect in RT was observed in all groups at both baseline and Week 8 measurements, which is similar to previously published literature in HC and MDD (Chechko et al., 2009; Cheng et al., 2015; Etkin et al., 2006; Etkin & Schatzberg, 2011; Fournier et al., 2017; Wortinger et al., 2017). With respect to emotional Stroop in accuracy, at baseline this was observed in HC, MDD-8 and MDD-16 and reflects previously published findings in MDD and HC (Etkin et al., 2006; Favre et al., 2015; Fournier et al., 2017; Rey et al., 2014; Torres-Quesada et al., 2014). By Week 8, only HC and MDD-8 demonstrated emotional Stroop in accuracy. The only between group difference in accuracy was observed between HC and MDD-8 at Week 8, with MDD-8 demonstrating lower accuracy overall and on congruent trials, but not on incongruent trials. This discrepancy is important in that it advances the idea that

the accuracy difference may be attributed to impaired emotion recognition in the MDD-8 group, rather than disinhibition in responding or to a speed/accuracy trade-off. In terms of neural activation, on all baseline comparisons of MDD groups with HC, reduced levels of neural activity were observed in multiple regions. These findings were contrary to our prediction of greater baseline neural activity in MDD groups. By comparison, other groups have found either increased activity in unmedicated MDD compared to HC (Etkin & Schatzberg, 2011) or no between group differences (Fournier et al., 2017) on an Emotional Conflict Task. In spite of the observed lower neural activity in MDD-8, there were no differences observed in behavioural responding on the Emotional Conflict Task. However, by Week 8 post treatment initiation, no differences in neural activity between MDD groups and HC were observed, which may be attributed to the treatment with escitalopram. Even though the reduction in mood symptoms was variable between the MDD-8, MDD-16 and MDD-NR groups, by Week 8, the differences in neural activation between the HC group and MDD groups respectively, was no longer significant. Within group, there was a reduction observed in neural activation in both HC and MDD-NR groups between baseline and Week 8, without a corresponding change in RT or accuracy, advancing the idea that this may demonstrate habituation on the emotion recognition task (Fischer et al., 2003; Spohrs et al., 2018), and that altered activity levels cannot be attributed to a significant learning effect. We were unable to differentiate the MDD-16 group from HC and MDD-8 at baseline or Week 8, or to characterize adequately why

this group of patients with MDD responded to later adjunctive treatment with atypical antipsychotic aripiprazole.

With respect to strengths, this is the first study to investigate the influence of escitalopram treatment on behavioural and neural responding in an Emotional Conflict Task, and the first study to explore longitudinal within participant performance on an Emotional Conflict Task. In addition to this, there were sufficient numbers of participant to retrospectively divide the MDD group into treatment remitters at Week 8, Week 16 or treatment non-remitters to examine the value of performance on the Emotional Conflict Task as a predictive marker of treatment response.

With regard to limitations, it may be that we were unable to demonstrate the emotional Stroop effect in accuracy in MDD-16 and MDD-NR at Week 8 due to possible ceiling effects or as a consequence of large degree of variability in responding within group. A further limitation, previously mentioned, is that we did not include a neutral category in the Emotional Conflict Task. Observing how changes in emotion context insensitivity or improvement in mood symptoms alter processing of neutral stimuli may have provided valuable information in how emotion recognition may be altered in response (or non-response) to antidepressant treatment. It has been reported that compared to HC, participants with MDD find it more challenging to correctly identify neutral or ambiguous expressions of emotion (Leppänen et al., 2004) and respond with altered neural activity in response to faces with neutral expressions (Oliveira et al., 2013). For

some patients with MDD, these differences may persist well into remission (Leppänen et al., 2004). Future work in MDD and emotion recognition should include an Emotional Conflict Task that includes varying degrees of emotional valence, including a neutral category, with sufficient power to allow for grouping of participants on sub-domains with respect to medication response and behavioural and neural responding.

Notwithstanding the above, this study provided important evidence in terms of the dissociation of the effects of escitalopram on processing of emotionally valenced stimuli in patients in MDD-8, MDD-16 and MDD-NR groups. While mood symptoms did improve in all MDD groups across time after receiving treatment with escitalopram, they did so to varying degrees. While the MDD-8 group had the fastest response to escitalopram treatment, emotional information processing actually became worse across time, providing evidence that improvements in mood do not necessarily translate to improvements in cognition (Zuckerman et al., 2018). A randomized trial of escitalopram treatment on cognitive functioning in stroke patients compared to Problem Solving Therapy also found improvements in global cognitive functioning were independent of changes in mood symptoms in the group receiving escitalopram treatment (Jorge et al., 2010). Finally, in the International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial comparison of 1008 patients with MDD receiving either escitalopram, sertraline or venlafaxine extended-release acute treatment, did not improve verbal memory, information processing, decision speed, response

inhibition or attention, regardless of treatment group, even in patients reaching remission (Shilyansky et al., 2016). Taken together, this suggests that while escitalopram may improve mood symptoms, more research is needed to find treatments that specifically target cognitive impairment in MDD to provide a pathway to functional remission (Shilyansky et al., 2016; Zuckerman et al., 2018). Additionally, findings in the MDD-8 group are contrary to the hypothesis that improvements in emotional information processing provide the context/are necessary for future improvements in mood symptoms in MDD (Godlewska et al., 2016; Harmer & Cowen, 2013; Tranter et al., 2009). This study also provided evidence that even though there were varying degrees of mood symptom amelioration across MDD groups, measures of neural activity were not significantly different between MDD groups and HC following 8 weeks of escitalopram treatment, suggesting that escitalopram treatment may have helped to normalize neural responding on an emotional conflict task. Finally, the baseline lower levels of neural activity in response to emotional information processing in all three MDD groups provides evidence for the emotion context insensitivity theory (Rottenberg, 2005). A calculated decrease in engagement with external emotional stimuli may occur as a preventative measure, to decrease the possibility of experiencing negative consequences and to diminish the changes of making unfortunate choices (Rottenberg, 2005) or simply to reduce energy expenditures (Maes et al., 2012).

Finally, Chapter 6 presented a case study of a male patient with longstanding hydrocephalus, referred for care to a tertiary psychiatric facility due to changes in behaviour and low mood symptoms. The study objective was to quantify the degree of ventriculomegaly in the participant and describe the primarily psychiatric and mood-related challenges the patient was facing, in spite of the extreme degree of ventriculomegaly. Investigations indicated a patient with some preserved functioning, with overt ventriculomegaly with gross dilation of the lateral and third ventricles coupled with an unremarkable neurological exam, and a borderline intelligence quotient, whose main complaints were psychiatric in nature. The patient presented with a ventricular volume close to 46 times larger than the estimated ventricular volume of male healthy control participants.

One of the strengths of this research is that with the available imaging technology we were able to quantify the excessive neurological remodeling in this patient, in contrast to previous case reports of long-standing overt ventriculomegaly (Canu et al., 2005; Feuillet et al., 2007; Lewin, 1980). Importantly, we were also able to highlight that psychiatric and mood symptoms may emerge when cognitive resources are challenged, as may be the case in patients with extreme neural remodeling.

A limitation in this case is that we were not able to complete functional testing with the participant or additional cognitive testing that may have shed light on emotional information processing in this participant, such as with the Emotional Conflict Task. Although the findings may have been interesting, given

the extreme structural remodeling, it would have been difficult to process and interpret the functional neuroimaging results.

Nevertheless, this was a unique contribution in that it appears to be the first paper to volumetrically quantify the degree of extreme ventriculomegaly in a patient with long-standing overt hydrocephalus presenting primarily with mood and psychiatric symptoms. While overtly the patient appeared with a relatively normal phenotype, this case demonstrates the brain's potential for adaptability and plasticity in the face of extreme structural stress and underlines the importance of exploring the possibility of a physiological cause when assessing psychiatric and cognitive complaints.

Taken together, the body of research presented here broadens our current understanding of neuroplasticity in MDD (Liu et al., 2017; McEwen et al., 2012), and contributes to the body of work supporting the emotion context insensitivity hypothesis (Bylsma et al., 2008; Rottenberg, 2005).

Specifically, this body of work demonstrates that i) changes in functional hippocampal activity are present early in the development of MDD in medication naïve patients presenting for MDD treatment for the first time, even when behavioural changes have not been observed. ii) In a group of midlife women receiving ET for perimenopausal symptoms, incongruent adaptation in RT and the reversal in the expected response facilitation in ATD, together with reduced neural activity in regions important for processing of emotional information, suggests that serotonin availability may be important for the processing of

conflicting emotional information. iii) Increased neural activity in ATD compared to Sham, without attendant differences in behavioural performance suggests supplementary neural regions may be enlisted to compensate for changes in neural activation attendant to a reduction in available serotonin, to attain levels of responding similar to those observed in the Sham condition, iv) Overall lower accuracy in an MDD group and an overall reduction in neural activity compared to HC (including neural regions associated with emotional conflict resolution, emotion recognition and processing of facial information), provides evidence that emotional information processing in MDD is different compared to HC. The lack of difference in behavioural or neural processing of happy versus fearful faces in an unmedicated MDD group provides evidence that emotional information processing in MDD is not biased towards either fearful or happy faces, but generally insensitive to emotion overall, and provides support for the emotion context insensitivity hypothesis (Rottenberg et al., 2005). v) Regardless of remission definition, all MDD groups (MDD-8 MDD-16 and MDD-NR) demonstrated lower levels of neural activity, compared to HC at baseline. Escitalopram ameliorated neural activity differences between HC and MDD groups by 8 weeks post treatment begin, even while reductions in mood symptoms across the groups remained variable. Specifically, in the MDD-8 group that reached the definition of treatment remission by Week 8, emotional information processing was worse at Week 8, while no changes in emotional cognition were observed in either MDD-16 or MDD-NR groups at the same time

point, indicating that changes in mood do not necessarily directly correlate with changes in cognition. vi) A patient may present overtly with a normal phenotype, even in spite of extreme neural remodeling due to structural stress. This case quantitatively described the extremes of the structural remodeling and underlined that the advantage of pluripotentiality in cases of extreme structural remodeling, may come at the expense of taxing the cerebral reserve, which could result in emergence of mood symptoms.

There are important clinical implications arising from this research. With the knowledge that hippocampal functioning is different in medication naïve patients with MDD compared to HC, future longitudinal research may seek to simultaneously track changes in neural functioning and morphometry within an MDE as well as across MDEs in patients that experience recurrent episodes of MDD. While some of our findings in MDD complemented previously published research, some of our findings were opposite to what may have been predicted based on the literature. There are important conclusions that may be drawn from this observation. Specifically, it is important to note that in the studies examining MDD patients, while all the participants in the MDD-8, MDD-16 and MDD-NR groups met criteria for the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) (American Psychiatric Association, 2014) definition of MDD, each group presented a different response phenotype in terms of escitalopram response, improvements in mood symptoms, and emotion recognition ability. These findings are noteworthy in the context of the National

Institute of Mental Health's Research Domain Criteria initiative (RDoC), which aims to develop a trans-diagnostic classification system that integrates evidence across multiple domains including genetics and neuroscience (Insel et al., 2010). Based on the findings of this body of research, development of treatment regimens or drug discovery could well include the cross-disorder sub-domain of behavioural and neural differences in emotion recognition (McIntyre, 2014). Further to this, considering the heterogeneous MDD response phenotypes, future research involving an MDD sample large enough to stratify participants on specific symptom presentation (e.g. hypersomnia versus insomnia, psychomotor slowing versus agitation, significant weight gain versus significant weight loss, etc.), rather than grouping together participants that have symptoms on opposite ends of a spectrum of specific MDD symptom, or who meet a numerical cut off on an MDD rating scale, may improve the stability and generalizability of findings. This, in turn, would provide richer details necessary for identifying a predictive treatment response biomarker for MDD. A reduction in the immediate availability in serotonin in women with perimenopause does not increase negative mood or vasomotor symptoms, but can affect neural processing of emotional information, and result in the recruitment of additional neural regions to attain levels of responding similar to a Sham condition. Future research should compare the effects of ATD and a Sham condition on emotional information processing and mood and vasomotor symptoms in perimenopausal women prior to receiving ET and after receiving ET. It may be interesting to further divide this sample and

characterize the women who derive an antidepressant benefit from ET, and the women who do not, as little research has been completed in this direction. Finally, with respect to the findings of mood symptoms in the patient with long-standing overt ventriculomegaly, as has been suggested by other authors (Canu et al., 2005), it is important to consider that some redundancy or reserve may be relegated to the cerebellum, or that the spared cortex may be densely packed and stretched rather than destroyed, in the case of an extremely slowly developing hydrocephalus.

To summarize, the current collection of research complements and broadens the current collection of knowledge pertaining to neuroplasticity in depression in a number of key areas. This research demonstrates that i) changes in neural function set patients with MDD apart from HC, even in early stages of disease progression, suggesting that functional changes may predate morphometric changes, ii) compared to HC, on an emotional conflict task, unmedicated patients with MDD exhibit lower levels of functional activity in regions important for processing emotional information, iii) that antidepressant treatment with escitalopram ameliorates difference in neural function between HC and MDD, even in patients that do not experience significant improvements in mood symptoms with escitalopram treatment, iv) treatment with a high dose of transdermal estradiol may effect longer lasting changes in serotonergic functioning, such as by increased serotonin receptor density, which are not as likely to be influenced by the acute decrease in serotonin availability as occurs in

the ATD paradigm, and v) the brain, with a great capacity for plasticity and adaptability, is capable of generating a normal phenotype even when experiencing serious structural stress. This work provides a range of unique and important findings to the discussion of functional and structural neuroplasticity in depression.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci,* 9, 357-381. doi:10.1146/annurev.ne.09.030186.002041

American Psychiatric Association. (2014). Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. Retrieved from https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm04

Bazin, N., Perruchet, P., De Bonis, M., & Feline, A. (1994). The dissociation of explicit and implicit memory in depressed patients. *Psychol Med,* 24(1), 239-245. doi:10.1017/S0033291700027008

Beck, A. T. (2002). Cognitive models of depression. In R. L. Leahy & E. T. Dowd (Eds.), *Clinical Advances in Cognitive Psychotherapy: Theory and Application* (pp. 29-61): Springer Publishing Company.

Belleau, E. L., Treadway, M. T., & Pizzagalli, D. A. (2019). The impact of stress and Major Depressive Disorder on hippocampal and medial prefrontal cortex morphology. *Biol Psychiatry,* 85(6), 443-453. doi:10.1016/j.biopsych.2018.09.031

Bhagwagar, Z., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2004). Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. *Am J Psychiatry,* 161, 166-168. doi:10.1176/appi.ajp.161.1.166

Boccardi, M., Ganzola, R., Bocchetta, M., Pievani, M., Redolfi, A., Bartzokis, G., . . . Frisoni, G. B. (2011). Survey of protocols for the manual segmentation of the hippocampus: preparatory steps towards a joint EADC-ADNI harmonized protocol. *J Alzheimers Dis,* 26 Suppl 3, 61-75. doi:10.3233/JAD-2011-0004

Bouhuys, A. L., Geerts, E., & Gordijn, M. C. (1999). Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. *J Nerv Ment Dis,* 187(10), 595-602. doi:10.1097/00005053-199910000-00002

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in Major Depression: a review. *Aust N Z J Psychiatry,* 44, 681-696. doi:10.3109/00048674.2010.496359

Buchsbaum, B. R., Olsen, R. K., Koch, P. F., Kohn, P., Kippenhan, J. S., & Berman, K. F. (2005). Reading, hearing, and the planum temporale. *Neuroimage,* 24(2), 444-454. doi:10.1016/j.neuroimage.2004.08.025

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in Major Depressive Disorder. *Clin Psychol Rev,* 28(4), 676-691. doi:10.1016/j.cpr.2007.10.001

Canu, E. D. G., Magnano, I., Paulus, K. S., Piras, M. R., Conti, M., Costantino, S., . . . Aiello, I. (2005). Neuropsychophysiological findings in a case of long-standing overt ventriculomegaly (LOVA). *Neuroscience Letters,* 385(1), 24-29. doi:10.1016/j.neulet.2005.05.026

Chechko, N., Kellermann, T., Schneider, F., & Habel, U. (2014). Conflict adaptation in emotional task underlies the amplification of target. *Emotion,* 14(2), 321-330. doi:10.1037/a0035208

Chechko, N., Wehrle, R., Erhardt, A., Holsboer, F., Czisch, M., & Samann, P. G. (2009). Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder. *PLoS One,* 4(5), e5537. doi:10.1371/journal.pone.0005537

Cheng, P., Preston, S. D., Jonides, J., Mohr, A. H., Thummala, K., Casement, M., . . . Deldin, P. J. (2015). Evidence against mood-congruent attentional bias in Major Depressive Disorder. *Psychiatry Res,* 230(2), 496-505. doi:10.1016/j.psychres.2015.09.043

Clayson, P. E., & Larson, M. J. (2013). Adaptation to emotional conflict: evidence from a novel face emotion paradigm. *PLoS One,* 8(9), e75776. doi:10.1371/journal.pone.0075776

Demarin, V., Morović, S., & Béné, R. (2014). Neuroplasticity. *Periodicum Biologorum,* 116(2), 209-211. Retrieved from <Go to ISI>://WOS:000341406500015

Dillon, D. G., & Pizzagalli, D. A. (2018). Mechanisms of memory disruption in depression. *Trends Neurosci,* 41(3), 137-149. doi:10.1016/j.tins.2017.12.006

Dukart, J., & Bertolino, A. (2014). When structure affects function--the need for partial volume effect correction in functional and resting state magnetic resonance imaging studies. *PLoS One,* 9(12), e114227. doi:10.1371/journal.pone.0114227

Dusi, N., Barlati, S., Vita, A., & Brambilla, P. (2015). Brain structural effects of antidepressant treatment in Major Depression. *Current neuropharmacology,* 13(4), 458-465. doi:10.2174/1570159X1304150831121909

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron,* 51(6), 871-882. doi:10.1016/j.neuron.2006.07.029

Etkin, A., & Schatzberg, A. F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in Generalized Anxiety and Major Depressive Disorders. *Am J Psychiatry,* 168(9), 968-978. doi:10.1176/appi.ajp.2011.10091290

Fairhall, S. L., Sharma, S., Magnusson, J., & Murphy, B. (2010). Memory related dysregulation of hippocampal function in Major Depressive Disorder. *Biol Psychiatry,* 85(3), 499-503. doi:10.1016/j.biopsycho.2010.09.002

Favre, P., Polosan, M., Pichat, C., Bougerol, T., & Baciu, M. (2015). Cerebral correlates of abnormal emotion conflict processing in euthymic bipolar patients: a functional MRI study. *PLoS One,* 10(8), e0134961-0134916. doi:10.1371/journal.pone.0134961

Feuillet, L., Dufour, H., & Pelletier, J. (2007). Brain of a white-collar worker. *Lancet,* 370(9583), 262. doi:10.1016/S0140-6736(07)61127-1

Finkelmeyer, A., Nilsson, J., He, J., Stevens, L., Maller, J. J., Moss, R. A., . . . McAllister-Williams, R. H. (2016). Altered hippocampal function in major depression despite intact structure and resting perfusion. *Psychol Med,* 46(10), 2157-2168. doi:10.1017/S0033291716000702

Fischer, H., Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2003). Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull,* 59(5), 387-392. doi:10.1016/s0361-9230(02)00940-1

Fournier, J., Chase, H., Greenberg, T., Etkin, A., Almeida, J., Stiffler, R., . . . Phillips, M. (2017). Neuroticism and individual differences in neural function in unmedicated Major Depression: findings from the EMBARC study. *Biol Psychiatry Cogn Neurosci Neuroimaging,* 2(2), 138-148. doi:10.1016/j.bpsc

Frey, B. N., Hall, G. B., Attard, S., Yucel, K., Skelin, I., Steiner, M., & Soares, C. N. (2010). Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point? *Menopause,* 17(4), 840-845. doi:10.1097/gme.0b013e3181df840f

Frodl, T., Jäger, M., Smajstrlova, I., Born, C., Bottlender, R., Palladino, T., . . . Meisenzahl, E. M. (2008). Effect of hippocampal and amygdala volumes on clinical outcomes in Major Depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci,* 33(5), 423-430. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18787661 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527720/

Godlewska, B. R., Browning, M., Norbury, R., Cowen, P. J., & Harmer, C. J. (2016). Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Transl Psychiatry,* 6(11), e957. doi:10.1038/tp.2016.130

Gold, A. L., Jarcho, J. M., Rosen, D. K., Pine, D. S., & Ernst, M. (2015). Emotional and nonemotional conflict processing in pediatric and adult anxiety disorders. *J Child Adolesc Psychopharmacol,* 25(10), 754-763. doi:10.1089/cap.2015.0066

Gordon, J. L., Girdler, S. S., Meltzer-Brody, S. E., Stika, C. S., Thurston, R. C., Clark, C. T., . . . Wisner, K. L. (2015). Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. *Am J Psychiatry,* 172(3), 227-236. doi:10.1176/appi.ajp.2014.14070918

Gotlib, I. H., Jonides, J., Buschkuehl, M., & Joormann, J. (2011). Memory for affectively valenced and neutral stimuli in depression: evidence from a novel matching task. *Cogn Emot,* 25(7), 1246-1254. doi:10.1080/02699931.2010.538374

Gualtieri, C. T., & Johnson, L. G. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol,* 21(7), 623-643. doi:10.1016/j.acn.2006.05.007

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci,* 368(1615), 20120407. doi:10.1098/rstb.2012.0407

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., & Sadato, N. (2001). Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed

by fMRI. *J Cogn Neurosci,* 13(8), 1035-1047. doi:10.1162/089892901753294338

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Doman Criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry,* 167(7), 748-751. doi:10.1176/appi.ajp.2010.09091379

Jorge, R. E., Acion, L., Moser, D., Adams, H. P., & Robinson, R. G. (2010). Escitalopram and enhancement of cognitive recovery following stroke. *Arch Gen Psychiatry,* 67(2), 187-196. doi:10.1001/archgenpsychiatry.2009.185

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci,* 17(11), 4302-4311. doi:10.1523/JNEUROSCI.17-11-04302.1997

Krug, M. K., & Carter, C. S. (2010). Adding fear to conflict: a general purpose cognitive control network is modulated by trait anxiety. *Cogn Affect Behav Neurosci,* 10(3), 357-371. doi:10.3758/CABN.10.3.357

Leppänen, J., Milders, M., Bell, J. S., Terriere, E., & Hietanen, J. K. (2004). Depression biases the recognition of emotionally neutral faces. *Psychiatry Res,* 128(2), 123-133. doi:10.1016/j.psychres.2004.05.020

Lewin, R. (1980). Is your brain really necessary? *Science,* 210(4475), 1232-1234. doi:10.1126/science.7434023

Liu, B., Liu, J., Wang, M., Zhang, Y., & Li, L. (2017). From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. *Front Cell Neurosci,* 11, 305. doi:10.3389/fncel.2017.00305

MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., . . . Young, L. T. (2003). Course of illness, hippocampal function, and hippocampal volume in Major Depression. *Proc Natl Acad Sci USA,* 100(3), 1387-1392. doi:10.1073/pnas.0337481100

MacQueen, G. M., Galway, T. M., Hay, J., Young, L. T., & Joffe, R. T. (2002). Recollection memory deficits in patients with Major Depressive Disorder predicted by past depressions but not current mood state or treatment status. *Psychol Med,* 32(2), 251-258. doi:10.1017/S0033291701004834

Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Galecki, P., & Leonard, B. (2012). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med,* 10, 66. doi:10.1186/1741-7015-10-66

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annu Rev Neurosci,* 22(1), 105-122. doi:10.1146/annurev.neuro.22.1.105

McEwen, B. S., Eiland, L., Hunter, R. G., & Miller, M. M. (2012). Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology,* 62(1), 3-12. doi:10.1016/j.neuropharm.2011.07.014

McIntyre, R. S. (2014). A vision for drug discovery and development: novel targets and multilateral partnerships. *Adv Ther,* 31(3), 245-246. doi:10.1007/s12325-014-0105-0

Menke, A. (2019). Is the HPA axis as target for depression outdated, or is there a new hope? *Front Psychiatry,* 10, 101. doi:10.3389/fpsyt.2019.00101

Milne, A. M., MacQueen, G. M., & Hall, G. B. (2012). Abnormal hippocampal activation in patients with extensive history of Major Depression: an fMRI study. *J Psychiatry Neurosci,* 37(1), 28-36. doi:10.1503/jpn.110004

mindhive: A community portal for MIT brain research. (2008, 30 April 2008 18:58). Frequently Asked Questions - Region-of-Interest (ROI) analysis. Retrieved from http://mindhive.mit.edu/node/101

Moses-Kolko, E. (2003). Widespread increases of cortical serotonin type 2A receptor availability after hormone therapy in euthymic postmenopausal women. *Fertility and Sterility,* 80(3), 554-559. doi:10.1016/s0015-0282(03)00973-7

Nagy, K., Greenlee, M. W., & Kovacs, G. (2012). The lateral occipital cortex in the face perception network: an effective connectivity study. *Front Psychol,* 3, 141. doi:10.3389/fpsyg.2012.00141

Nieto-Castanon, A., Ghosh, S. S., Tourville, J. A., & Guenther, F. H. (2003). Region of interest based analysis of functional imaging data. *Neuroimage,* 19(4), 1303-1316. doi:10.1016/s1053-8119(03)00188-5

Oliveira, L., Ladouceur, C. D., Phillips, M. L., Brammer, M., & Mourao-Miranda, J. (2013). What does brain response to neutral faces tell us about Major

Depression? Evidence from machine learning and fMRI. *PLoS One,* 8(4), e60121. doi:10.1371/journal.pone.0060121

Parvizi, J., Jacques, C., Foster, B. L., Witthoft, N., Rangarajan, V., Weiner, K. S., & Grill-Spector, K. (2012). Electrical stimulation of human fusiform face-selective regions distorts face perception. *J Neurosci,* 32(43), 14915-14920. doi:10.1523/JNEUROSCI.2609-12.2012

Persad, S. M., & Polivy, J. (1993). Differences between depressed and nondepressed individuals in the recognition and response to facial emotional cues.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat Rev Neurosci,* 9(2), 145-158. doi:10.1038/nrn2317

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J Neurosci,* 28(36), 8929-8933. doi:10.1523/JNEUROSCI.1450-08.2008

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology,* 33(1), 88-109. doi:10.1038/sj.npp.1301574

Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *J Neurosci,* 18(6), 2188-2199. doi:10.1523/JNEUROSCI.14-03-01450.1994

Rey, G., Desseilles, M., Favre, S., Dayer, A., Piguet, C., Aubry, J.-M., & Vuilleumier, P. (2014). Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: preliminary findings from a follow-up state-based fMRI study. *Psychiatry Res,* 223(2), 84-93. doi:10.1016/j.pscychresns.2014.04.016

Roddy, D. W., Farrell, C., Doolin, K., Roman, E., Tozzi, L., Frodl, T., . . . O'Hanlon, E. (2019). The hippocampus in depression: more than the sum of its parts? Advanced hippocampal substructure segmentation in depression. *Biol Psychiatry,* 85(6), 487-497. doi:10.1016/j.biopsych.2018.08.021

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS Spectrums,* 18(3), 139-149. doi:10.1017/S1092852913000072

Rottenberg, J. (2005). Mood and emotion in Major Depression. *Curr Dir Psychol Sci,* 14(3), 167-170. doi:10.1111/j.0963-7214.2005.00354.x

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in Major Depressive Disorder. *J Abnorm Psychol,* 114(4), 627-639. doi:10.1037/0021-843X.114.4.627

Rybaczyk, L. A., Bashaw, M. J., Pathak, D. R., Moody, S. M., Gilders, R. M., & Holzschu, D. L. (2005). An overlooked connection: serotonergic mediation of estrogen-related physiology and pathology. *BMC Women's Health,* 5(1). doi:10.1186/1472-6874-5-12

Scheele, D., Mihov, Y., Schwederski, O., Maier, W., & Hurlemann, R. (2013). A negative emotional and economic judgment bias in Major Depression. *Eur Arch Psychiatry Clin Neurosci,* 263(8), 675-683. doi:10.1007/s00406-013-0392-5

Schmaal, L., Veltman, D. J., van Erp, T. G., Samann, P. G., Frodl, T., Jahanshad, N., . . . Hibar, D. P. (2015). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry,* 21(6), 806-812. doi:10.1038/mp.2015.69

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry,* 3(5), 425-435. doi:10.1016/s2215-0366(16)00012-2

Spohrs, J., Bosch, J. E., Dommes, L., Beschoner, P., Stingl, J. C., Geiser, F., . . . Viviani, R. (2018). Repeated fMRI in measuring the activation of the amygdala without habituation when viewing faces displaying negative emotions. *PLoS One,* 13(6), e0198244. doi:10.1371/journal.pone.0198244

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex,* 45(9), 1091-1096. doi:10.1016/j.cortex.2008.12.004

Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in Major Depression: a systematic review of neuroimaging findings. *Biol Mood Anxiety Disord,* 1(1), 10. doi:10.1186/2045-5380-1-10

Torres-Quesada, M., Korb, F. M., Funes, M. J., Lupiáñez, J., & Egner, T. (2014). Comparing neural substrates of emotional vs. non-emotional conflict

modulation by global control context. *Front Hum Neurosci,* 8, 1-14. doi:10.3389/fnhum.2014.00066

Tranter, R., Bell, D., Gutting, P., Harmer, C., Healy, D., & Anderson, I. M. (2009). The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. *J Affect Disord,* 118(1-3), 87-93. doi:10.1016/j.jad.2009.01.028

Wessa, M., & Lois, G. (2015). Brain functional effects of psychopharmacological treatment in Major Depression: a focus on neural circuitry of affective processing. *Current neuropharmacology,* 13(4), 466-479. doi:10.2174/1570159X13666150416224801

Wortinger, L. A., Endestad, T., Melinder, A. M., Oie, M. G., Sulheim, D., Fagermoen, E., & Wyller, V. B. (2017). Emotional conflict processing in adolescent chronic fatigue syndrome: a pilot study using functional magnetic resonance imaging. *J Clin Exp Neuropsychol,* 39(4), 355-368. doi:10.1080/13803395.2016.1230180

Yucel, K., Taylor, V. H., McKinnon, M. C., Macdonald, K., Alda, M., Young, L. T., & MacQueen, G. M. (2008). Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology,* 33(2), 361-367. doi:10.1038/sj.npp.1301405

Zuckerman, H., Pan, Z., Park, C., Brietzke, E., Musial, N., Shariq, A. S., . . . McIntyre, R. S. (2018). Recognition and treatment of cognitive dysfunction in Major Depressive Disorder. *Front Psychiatry,* 9, 655. doi:10.3389/fpsyt.2018.00655