EXPLICIT EMOTIONAL MEMORY IN MAJOR DEPRESSIVE DISORDER DURING CLINICAL REMISSION

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

Descriptive Note

MASTER OF SCIENCE (2019) McMaster University

Hamilton, Ontario, CANADA

DEPARTMENT:	Neuroscience
TITLE:	Explicit Emotional Memory in Major Depressive Disorder During Clinical Remission
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NUMBER OF PAGES:	xiii, 132

Lay Abstract

Major depressive disorder (MDD) is one of the most common mental disorders worldwide. It is estimated that over 10% of Canadians will experience MDD at some point in their lifetime. The symptoms of MDD include, among other things: depressed mood, loss of interest in regular daily activities, and impairments in cognition (e.g., attention, emotion, memory, etc.). Clinicians and researchers have argued for years that MDD is associated with negative cognitive biases, including increased attention to, and more accurate memory for, negative information; however, attention, emotion and memory are *general* forms of cognition, and the existence of cognitive biases for *specific* sub-domains of cognition in MDD are largely unknown. Given that MDD has a negative effect on emotion and memory, one potentially important sub-domain of cognition is explicit emotional memory (EM; i.e., conscious memory for emotionally-stimulating information). The purpose of the current thesis was to investigate whether MDD, during both the active (i.e., acute) and euthymic (i.e., clinically-remitted) stages, is associated with explicit EM biases compared to healthy volunteers. This thesis discusses how patterns of explicit EM may be important for our understanding of the development of MDD.

Abstract

This thesis comprises research investigating explicit EM biases in MDD during acute depression and euthymia (i.e., clinical remission). First, a systematic review was conducted to investigate whether acutely depressed and euthymic MDD participants display an explicit EM bias. An 'explicit EM bias' was operationally defined to denote enhanced memory for negative or positive stimuli compared to matched healthy controls (HCs). Studies that were included in this systematic review investigated explicit EM using free recall and recognition memory paradigms. The main finding from this investigation was that acutely depressed MDD participants do not display an explicit EM bias. An unintended consequence of this investigation was the identification that research on explicit EM in MDD during euthymia is surprisingly sparse. Next, building upon the findings from our systematic review, we conducted an empirical investigation of explicit EM within a sample of well-characterized euthymic MDD participants compared to age/sex/gender/IQ-matched HCs. In this study, participants performed incidental encoding (i.e., emotional reactivity) and recognition memory tasks (separated by one week). These tasks employed emotionally-valent picture stimuli obtained from the International Affective Picture System. Results from this study revealed that, compared to matched HCs, euthymic MDD participants do not display an emotional reactivity or explicit EM bias. Taken together, the findings from this thesis suggest that explicit EM represents a sub-domain of cognition that may be unaffected in individuals with MDD. Our findings have important implications for the unified model of depression and may represent a basis upon which future research can build in an attempt to understand the nuanced cognitive phenotypes associated with MDD.

Acknowledgements

I would like to thank my supervisors, Drs. Benicio Frey and Flávio Kapczinski, along with my committee members, Drs. Randi McCabe and Margaret McKinnon, for their continued support, mentorship and professional insights on the collection of work included within this thesis. I would also like to acknowledge several individuals for their support on this research since its inception: Monisha Persaud, Sabrin Salim and Maha Eltayebani. Finally, I would like to thank my family and friends for their continued support and encouragement throughout the entirety of my graduate studies.

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List of Abbreviations

ANCOVA: analysis of covariance
BD: bipolar disorder
BDI: Beck Depression Inventory
BRIAN: Biological Rhythms Interview Assessment for Neuropsychiatry
CCHS: Canadian Community Health Survey
CTQ: Childhood Trauma Questionnaire
DASS: Depression Anxiety Stress Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EM: emotional memory
EPHPP: Effective Public Health Practice Project
ER: emotional reactivity
fMRI: functional magnetic resonance imaging
HC: healthy control
HDRS: Hamilton Depression Rating Scale
HPA: hypothalamic-pituitary-adrenal
IAPS: International Affective Picture System
ICD: International Classification of Diseases
IM: implicit memory
MADRS: Montgomery-Åsberg Depression Rating Scale
MDD: major depressive disorder
MDE: major depressive episode
MRI: magnetic resonance imaging
MTL: medial temporal lobe
PCL-5: PTSD Checklist for DSM-5
PFC: pre-frontal cortex
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI: Pittsburgh Sleep Quality Index
SAM: self-assessment manikin
SCID: Structured Clinical Interview for DSM Disorders
SCID-5-CV: Structured Clinical Interview for DSM-5 Disorders, Clinician Version
STAI: State-Trait Anxiety Inventory
STICSA: State-Trait Inventory for Cognitive and Somatic Anxiety
WASI: Wechsler Abbreviated Scale of Intelligence
WHO: World Health Organization
WTAR: Wechsler Test of Adult Reading
YMRS: Young Mania Rating Scale

Declaration of Academic Achievement

Dr. Benicio Frey, Ms. Monisha Persaud and I were responsible for the development of the research questions associated with the systematic review and primary research included in Chapters 2 and 3 of this thesis, respectively. Drs. Benicio Frey, Flávio Kapczinski, Randi McCabe, Margaret McKinnon and I were responsible for the development of the research question associated with the primary research presented in Chapter 4.

Concerning the systematic review presented in Chapter 2, I was responsible for: defining the study methodology; registering the systematic review with PROSPERO (ID: CRD42017069909); assisting in the development of the search strategy; screening collected articles; extracting and analyzing data from eligible studies; and preparing and revising the manuscript. Ms. Monisha Persaud was also responsible for: defining the study methodology; registering the systematic review with PROSPERO; assisting in the development of the search strategy; screening collected articles; extracting and analyzing data from eligible studies; and preparing the manuscript. Ms. Denise Smith was involved with the development and implementation of the search strategy. Drs. Benicio Frey and Flávio Kapczinski were involved with the critical editing of the manuscript.

Concerning the primary research presented in Chapters 3 and 4, I was responsible for overseeing all study-related tasks, including: obtaining ethical approval from the Hamilton Integrated Research Ethics Board; recruiting and screening participants; collecting, analyzing and interpreting all data; implementing all changes from the amended protocol (see Chapter 4); and writing the manuscript. Ms. Monisha Persaud assisted with obtaining ethical approval, screening participants and collecting data. Ms. Sabrin Salim assisted with screening participants

and collecting data. Dr. Maha Eltayebani assisted with the screening of participants. Ms. Jee Su Suh provided recommendations and support regarding statistical procedures. Drs. Benicio Frey, Flávio Kapczinski, Randi McCabe and Margaret McKinnon provided continued supervision and oversight of this study, which included critical review of the manuscript presented in Chapter 3.

CHAPTER 1

General Introduction

Depression was recently identified by the World Health Organization (WHO) as a global health crisis (Marcus et al., 2012). Depression, clinically-defined as major depressive disorder (MDD; National Institute of Mental Health, 2018), is a heterogeneous illness that profoundly affects one's mood, psychosocial functioning, and quality of life. MDD is a highly prevalent classification of depression with explicitly-defined diagnostic criteria (American Psychiatric Association, 2013). A common and reliable symptom of MDD is cognitive dysfunction. *General* dysfunction across several domains of cognition in MDD during acute depression and euthymia (i.e., clinical remission) has been the topic of a significant body of literature (see, for example, Pan et al., 2019); however, a comparably small amount of research has been devoted to investigating functioning across *specific* sub-domains of cognition in MDD during both stages of the illness. Consequently, little is known about how the phenotypes of specific cognitive sub-domains differ in MDD between acute depression and euthymia. Research investigating sub-domains of cognition in MDD may: (1) inform our theoretical understanding of the cognitive nature of MDD; and (2) inform non-pharmacological, cognitive-based therapeutic treatment approaches aimed at improving clinical outcomes.

The current work sought to investigate the patterns of cognitive performance in MDD during acute depression and euthymia for the cognitive sub-domain of explicit emotional memory (EM). Chapter 1 provides: (1) general background information on MDD; (2) a review of the unified model of depression; (3) a discussion of general cognitive functioning in MDD during a major depressive episode (MDE) and during euthymia; and (4) a discussion of the

mechanisms underlying explicit EM formation. Chapter 2 includes a systematic review of the scientific literature on the topic of explicit EM in mood disorders—including MDD and bipolar disorder—during an acute mood episode and during euthymia. This systematic review discusses the need for further research on explicit EM in MDD, especially during euthymia. Chapter 3 includes the final manuscript of our primary research on emotional reactivity and explicit (episodic) EM in MDD during euthymia. In Chapter 4, a follow-up study to the original work presented in Chapter 3 is discussed. This follow-up study involves introducing personal relevance and subjective valence categorization as factors in the investigation of explicit EM in MDD. Chapter 4 includes a brief discussion of the influence of these phenomena on explicit EM, the methodology of the follow-up study, preliminary results from the follow-up study, and a brief discussion about the potential influence of these factors on explicit EM in MDD. Finally, Chapter 5 concludes this thesis with a general discussion of the current work, the strengths and limitations of the current work, and the proposition of future research directions.

Major Depressive Disorder

MDD is one of the most prevalent mental disorders worldwide and represents the leading cause of global disability (World Health Organization, 2017). The WHO estimates that 4.4% of the global population (i.e., 322 million cases) has a history of MDD, with nearly 50 million cases in North and South America alone (World Health Organization, 2017). A recent population-based estimate from Canada helped conceptualize the high occurrence of MDD by providing a country-specific prevalence rate. For example, the Canadian Community Health Survey (CCHS) recently reported that, as of 2012, approximately 11.3% of Canadians present with a lifetime history of MDD, with 4.7% of Canadians experiencing an MDE within the past 12 months

(Government of Canada, 2016; Knoll & MacLennan, 2017; Patten et al., 2017). The high prevalence of MDD, along with its associated impairments in psychosocial functioning, translates into an annual economic burden of CAD$32.3 billion (The Conference Board of Canada, 2016).

MDD is classified as a mood disorder that involves the recurrence of MDEs. An MDE is defined by at least five of the following symptoms over a minimum of a single two-week period: (1) depressed mood; (2) loss of interest and/or pleasure in most previously enjoyable activities; (3) marked increase or decrease in appetite and/or weight; (4) reduced or agitated psychomotor functioning; (5) insomnia or hypersomnia; (6) loss of energy; (7) feelings of worthlessness or guilt; (8) impaired cognitive functioning; and (9) thoughts of death, suicidal ideation, a plan for completing suicide, and/or suicide attempt(s), where (1) or (2) *must* be present (American Psychiatric Association, 2013). These symptoms must occur most of the day, nearly every day, over a single two-week period, and the symptoms must cumulatively contribute to clinically-significant distress and/or impairment in psychosocial functioning (American Psychiatric Association, 2013). MDEs may also present with or without psychotic features.

In the replicated version of the National Comorbidity Survey, researchers found that a diagnosis of lifetime MDD occurred with a co-morbid mental disorder in 72.1% of cases, with an anxiety disorder and a substance use disorder present in 59.2% and 24.0% of cases, respectively (Kessler et al., 2003). Results from the CCHS further support the high incidence of co-morbid diagnoses with MDD by showing that a history of MDD among Canadians was commonly associated with a diagnosis of generalized anxiety disorder (39.2% of cases), alcohol abuse (19.5% of cases), alcohol dependence (8.6% of cases), drug abuse (cannabis: 12.4% of cases; other drugs: 5.9% of cases) and drug dependence (cannabis: 5.1% of cases; other drugs: 6.1% of

cases; Patten et al., 2015). The diagnosis of a co-morbid mental disorder with MDD can further exacerbate the severity of the illness and may increase the economic burden of MDD on the Canadian economy (Patten et al., 2015).

Estimates of the median age of onset of MDD range from 24 (Bromet et al., 2011) to 32 (Kessler et al., 2005). Several risk factors have been identified to contribute to an increased risk for developing MDD. For example, research consistently shows that females are approximately twice as likely as males to develop MDD (Albert, 2015; World Health Organization, 2017). Social risk factors that have been associated with the development of MDD include: social isolation, negative life events (i.e., loss of a loved one, financial instability, social challenges, etc.) and the exposure to childhood trauma and/or neglect (Otte et al., 2016; Wilson et al., 2014). Research investigating the biological underpinnings of MDD is an active area of research, with recent work identifying 44 genetic risk variants underlying the illness (Wray et al., 2018). The current opinion surrounding the genetic component of MDD is the watershed model proposed by Keller and Miller (2006). In this model, the symptoms of MDD manifest when many "upstream" genetic mutations interfere with "downstream" narrowly-defined mechanisms (e.g., monoaminergic neurotransmission; Keller & Miller, 2006; Ormel, Hartman & Snieder, 2019). Many of these affected narrowly-defined mechanisms cumulatively interact to modulate broader mechanisms (e.g., emotional memory) which, in turn, cumulatively interact to produce the phenotypic symptoms observed in MDD (e.g., depressed mood; Keller & Miller, 2006; Ormel, Hartman & Snieder, 2019). Regardless of its specific etiology, the clinical presentation of MDD can be quite heterogeneous with varying clinical severity.

Given that the prolonged effects of untreated MDD include changes in neural morphometry (i.e., reduced hippocampal volume, discussed later), it is important that the illness

is treated with an early, patient-centered approach (Oluboka et al., 2017). Clinicians and researchers both suggest that an early therapeutic intervention, such as first-line treatment with an antidepressant medication (Kennedy et al., 2016), may optimize clinical outcomes and accelerate the illness trajectory towards functional remission (Oluboka et al., 2017). Unfortunately, roughly 50% of patients with MDD do not respond to first-line treatment interventions, and 10-30% of patients develop treatment-resistant depression (McLachlan, 2018; Rush, 2007). Another complicating factor in the treatment of MDD involves the distinction between symptomatic and functional remission. It has been observed that symptomatic improvements may proceed improvements in functional capacity following treatment (Novick et al., 2018; Oluboka et al., 2017). Failure to return to baseline functional capacity has severe implications on one's psychosocial functioning and may represent a heightened risk for future relapse. Consequently, significant efforts have been directed towards identifying potential phenotypes that distinguish the active stage from the euthymic stage of MDD. This research, primarily focusing on cognitive phenotypes, may promote a better understanding of the state versus trait nature of the cognitive deficits associated with MDD, and may inform more accurate and targeted treatment interventions.

The Unified Model of Depression

The cognitive model of depression has been the prevailing model of depression for decades (Clark & Beck, 1999). This model has frequently been revised to accommodate new research findings (see, for example, Beck, 2008). Beck and Bredemeier completed the most recent revision of this model in 2016 by integrating new findings from clinical, cognitive, biological, and evolutionary research. In the newly revised model, termed the 'unified model of

depression' (summarized in Figure 1.1.), the presence of genetic mutations *and/or* exposure to childhood trauma and/or neglect may predispose individuals to the development of MDD (Beck & Bredemeier, 2016). These phenomena may lead to the development of negative information processing biases and/or heightened biological reactivity (i.e., dysregulation of the hypothalamic-pituitary-adrenal [HPA] axis, which may result in: increased release of cortisol; neural atrophy of the hippocampus; and/or heightened activation of the amygdala; Beck & Bredemeier, 2016). According to the model, the precipitating factor that may unleash the symptoms of MDD is "the *perceived* loss of an investment in a vital resource" (i.e., interpersonal relations and/or internal assets). Many stressors, including those discussed above, may impact one or more vital resources, which may in turn precipitate the development of MDD. According to the model, the experience of a stressor alone may not be enough to precipitate the symptoms of MDD; instead, the experience of a stressor *and* the perceived irreversible loss of one's investment in a vital resource in combination may make one particularly vulnerable to the development of MDD (Beck & Bredemeier, 2016). Consider, as an example, the death of a partner. Losing a partner would likely result in the perceived permanent loss of one's investment in a (presumably positive and emotionally-rewarding) interpersonal relationship. It is important to note that the precipitating factor relies on perceived loss; therefore, the extent to which a stressor influences one's vulnerability to developing MDD depends on one's subjective appraisal of how meaningful the loss of investment is to one or more of their vital resources.

The presence of maladaptive cognitive structures, called schemas, within which beliefs are set, may further predispose one to the development of MDD (Beck, 1974, 2008). A specific set of maladaptive schemas present in MDD, called the cognitive triad (Beck, 1976),

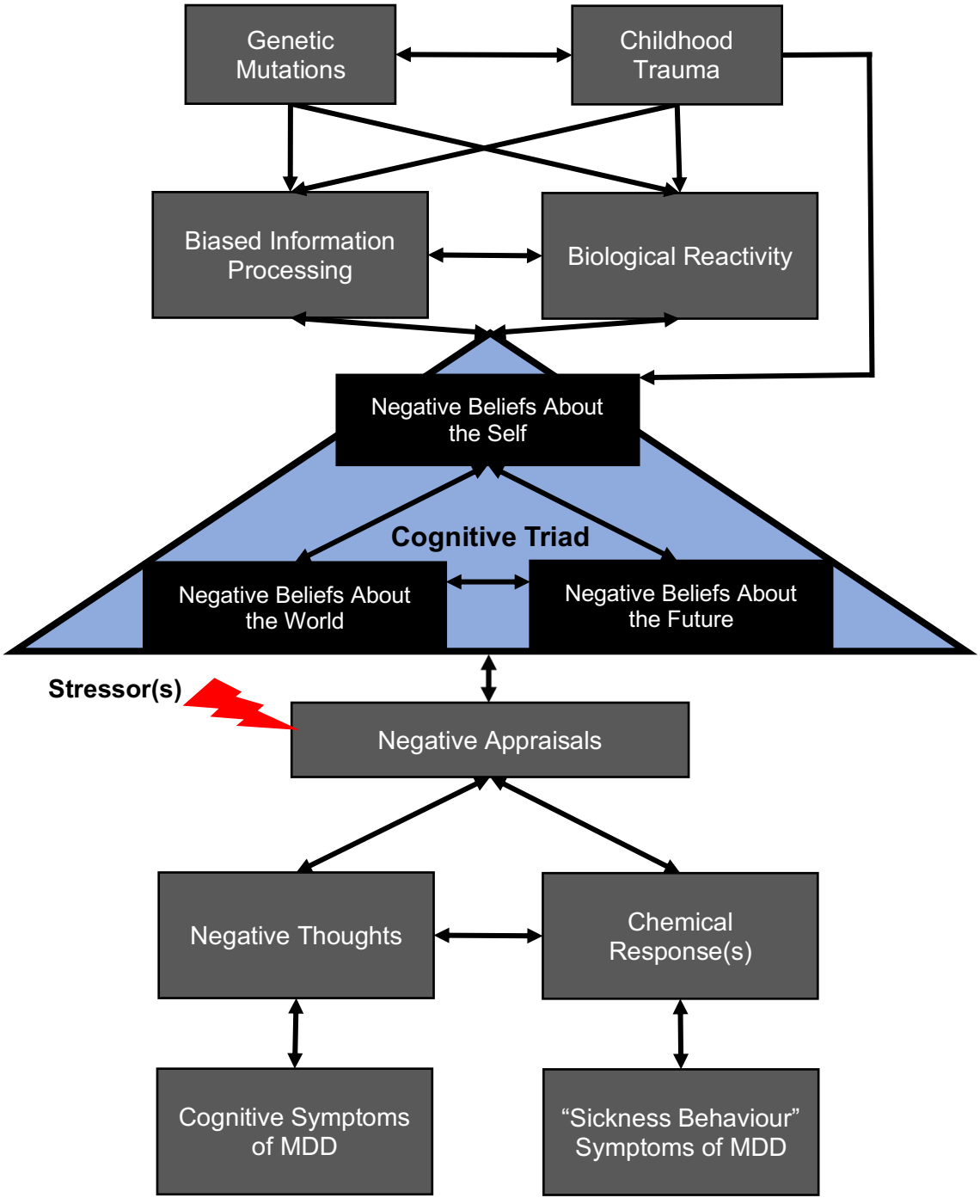

Figure 1.1. Summary of the unified model of depression. Adapted from Beck and Bredemeier (2016).

simultaneously interact in a feedback loop to make subjective appraisals about the environment and to inform subsequent behavioural responses in MDD (Beck, 2008; Beck & Bredemeier, 2016). These schemas include: (1) beliefs about the self (i.e., self-image); (2) beliefs about the world; and (3) beliefs/expectations about the future (Beck & Bredemeier, 2016). In MDD, these schemas are negatively-oriented; therefore, in response to a negative stressor, these maladaptive schemas may become activated—the extent of schematic activation dependent upon the salience of the stressor and the severity of depressive symptoms—and become dominate over positive schemas (Beck & Bredemeier, 2016). Activation of these schemas then result in negatively-biased information processing across several cognitive domains (i.e., attention, reactivity, memory, etc.), which results in the reinforcement of negative thoughts/beliefs, negative appraisals and depressive symptoms (Beck & Bredemeier, 2016). Negative appraisals may then lead to: (1) automatic negative thoughts, which are responsible for the cognitive symptoms of MDD; and/or (2) activation of the autonomic nervous system and immune system (also mediated by the neurotransmission of serotonin and dopamine), which results in the "sickness behaviours" observed in MDD (i.e., anhedonia, loss of energy, etc.; Beck & Bredemeier, 2016).

The symptoms of MDD can be explained by this model as an evolutionarily adaptive mechanism to conserve energy in response to the perceived loss of an investment in a vital resource (Beck & Bredemeier, 2016; Durisko et al., 2016). This energy conservation allows the body to withdraw energy from non-essential activities and processes in an attempt to promote survival (Beck & Bredemeier, 2016). This energy can then be directed towards tasks that will enhance the chances of survival while the individual attends to, and hypothesizes how to overcome, the circumstances surrounding the perceived loss of an investment in a vital resource (see, for example, Andrews & Thomson, 2009). This response may become so severe that it may

cause clinically-significant distress and/or impairment, leading to the clinical diagnosis of MDD (American Psychiatric Association, 2013; Beck & Bredemeier, 2016).

Cognitive Functioning in Major Depressive Disorder

According to the unified model of depression, maladaptive cognitive schemas predispose individuals with MDD to the development of cognitive dysfunction (Beck & Bredemeier, 2016). Indeed, the observation that MDD is associated with deficits in *general* domains of cognitive processing has been widely documented in the scientific literature (e.g., Gollan et al., 2008; Hammar & Årdal, 2009; Lam et al., 2014; Pan et al., 2019; Rock et al., 2014). For instance, research consistently shows that, compared to healthy controls (HCs), acutely depressed individuals with MDD exhibit impairments in the cognitive domains of: executive functioning, attention, emotional processing, psychomotor speed, learning, and memory (Gollan et al., 2008; Hammar & Årdal, 2009; Lam et al., 2014; Rock et al., 2014). These cognitive impairments may be understood as a result of an adaptive mechanism that draws energy away from cognitive processes that are non-essential to survival during an MDE (Beck & Bredemeier, 2016).

While some domains of cognitive dysfunction seem to improve following clinical remission from MDD, cognitive impairments have been observed in a significant proportion of individuals with MDD during clinical remission of symptoms. Recent systematic reviews and meta-analyses (e.g., Bora et al., 2012; Hasselbalch, Knorr & Kessing, 2011; Rock et al., 2014) have identified several areas of cognitive dysfunction that persist into the euthymic stage of MDD. For example, Bora et al. (2012) showed that euthymic participants with a history of MDD displayed significantly poorer global cognition (Cohen's $d = 0.47$), executive functioning (Cohen's $d = 0.59$), attention (Cohen's $d = 0.53$), processing speed (Cohen's $d = 0.47$), visual

memory (Cohen's $d = 0.54$), verbal memory (Cohen's $d = 0.48$) and working memory (Cohen's $d = 0.39$) compared to HCs. Interestingly, Rock et al. (2014) more recently found that, while euthymic MDD participants performed significantly worse than HCs on executive functioning (Cohen's d ranged from 0.53 – 0.61) and attention (Cohen's $d = 0.52$), there was no significant difference between groups on memory performance (Cohen's d ranged from 0.22 – 0.54); it should be noted, however, that the latter study by Rock et al. [2014] only included 7 studies with a sample of euthymic MDD participants, while the former study by Bora et al. [2012] included 27 studies with a sample of euthymic MDD participants). Furthermore, in their systematic review, Hasselbalch, Knorr, and Kessing (2011) similarly showed the existence of cognitive dysfunction in MDD during euthymia, with 9 out of 11 included studies reporting significantly worse performance among euthymic MDD participants compared to HCs on at least one assessment of executive functioning, attention, memory, and/or global cognition. These findings highlight that, although euthymic individuals with a history of MDD may be defined as euthymic on the basis of clinical evaluation, functionally, their cognitive performance in certain cognitive domains continues to fall short of that observed in HCs. This can be explained by the unified model of depression (see Figure 1.1.), which suggests that the maladaptive schemas that predisposed the individual to the development of MDD remain activated during euthymia, albeit to a lesser degree, resulting in continued cognitive impairment (Beck & Bredemeier, 2016).

Other clinically-relevant phenotypes in MDD that are suggested to result from the maladaptive, negatively-oriented cognitive schemas are negative information processing biases (Beck, 2008; Beck & Bredemeier, 2016). The unified model of depression posits the existence of at least two specific negative information processing biases in MDD: attention and memory biases (Beck, 2008; Beck & Bredemeier, 2016; Murrough et al., 2011). These biases are often

termed 'mood-congruent biases' to denote the simultaneous increased attention to, and memory for, negative information *and* the decreased attention to, and memory for, positive information (Trapp et al., 2018). In their meta-analysis of 29 studies, Peckham, McHugh, and Otto (2010) concluded that depressed participants display significantly greater attention towards negative information compared to HCs for the dot probe task (Cohen's $d = 0.52$), but not for the emotional Stroop task (Cohen's $d = 0.17$); however, it must be noted that these findings do not necessarily reflect the phenotype of MDD specifically given that the 'depressed' participants in this study included individuals with current MDD, current dysthymic disorder, self-reported dysphoria, and individuals who underwent a negative mood induction. Interestingly, a recent study by Elgersma et al. (2018) showed that "pure" MDD participants (i.e., participants with no co-morbid anxiety disorder) and MDD participants with a co-morbid anxiety disorder did not display a negative attention bias when compared to HCs on the Exogenous Cueing Task (cues: word stimuli). Similarly, Trapp et al. (2018) recently showed that MDD participants did not differ from HCs on attention biases using a dot probe task. These recent findings appear inconsistent with the unified model of depression and challenge the existence of a true mood-congruent, negative attention bias in MDD.

The existence of a mood-congruent negative EM bias in MDD is similarly controversial. Conceptually, memory is classified according to explicit (i.e., conscious) or implicit (i.e., unconscious) memory (Baddeley, 2001). Explicit memory is further sub-classified into semantic (i.e., factual) and episodic (i.e., biographical events; Baddeley, 2001). In a recent meta-analysis of 20 studies, Gaddy and Ingram (2014) reported that depressed individuals (i.e., clinically-depressed [MDD] and dysphoric participants combined) displayed a negative memory bias for implicit memory, and that several moderating factors (e.g., age, self-referent encoding strategy,

type of encoding and recall tasks, etc.) moderate this effect and may account for the inconsistent findings reported in the literature. Findings from research on the existence of biased autobiographical memory is also mixed, with some studies reporting that MDD is associated with impaired autobiographical memory for positive information compared to HCs (e.g., Lemogne et al., 2006) and others reporting the existence of a negative autobiographical memory bias (e.g., Köhler et al., 2015). The subject of non-autobiographical explicit memory in MDD is the topic of the remaining chapters of this thesis.

In conclusion, the existence of mood-congruent, negative attention and/or memory biases in MDD remain unclear. Investigation into the pattern(s) of cognitive bias(es) in sub-domains of cognitive processing may help elucidate the full cognitive profile of MDD.

Mechanisms of Explicit Emotional Memory Formation: Normal Physiology Versus Major Depressive Disorder

Under normal physiological conditions, humans tend to remember emotionally-arousing (i.e., negative and positive) information more accurately than unemotional (i.e., neutral) information (Cahill & McGaugh, 1998; Talmi, 2013). Indeed, Dolcos, LaBar, and Cabeza (2005) showed that, after a one-year delay between encoding and memory retrieval tasks, a small sample of female HC participants recognized significantly more emotional stimuli than unemotional stimuli. This phenotype is evolutionarily adaptive given that emotionally-arousing information, both negative and positive, is likely to signify a stimulus or event that is relevant to survival (Hamann, 2001). A myriad of research investigating the cognitive and neurological underpinnings of this observation has been conducted within HCs to help identify the cognitive processes and neural circuitry that exist under healthy conditions (Buckner & Koutstaal, 1998;

Cahill & McGaugh, 1998; Diamond et al., 2007; Dolcos, LaBar & Cabeza, 2005; Hamann, 2001; Kensinger & Corkin, 2004; LaBar, 2007; LaBar & Cabeza, 2006; Phelps, 2004; Talmi, 2013). This information may be useful in the understanding of cognitive, physiological and/or neural changes that may occur during MDD that might influence the manifestation and/or maintenance of the cognitive symptoms of the illness, including impairments in explicit EM.

The formation of EM follows a well-characterized sequence of three cognitive stages: (1) encoding (the development of the memory trace; i.e., through attention to, and elaboration of, the stimulus/information); (2) consolidation (strengthening and storage of the memory trace); and, in the case of explicit EM, (3) *conscious* retrieval (LaBar & Cabeza, 2006; Hamann, 2001). Research suggests that the process of consolidation is highly time-dependent, with a longer delay between encoding and retrieval tasks allowing for greater consolidation and, by extension, strengthening of the memory trace (Hamann, 2001; McGaugh, 2000). When the target stimulus/information is emotionally-arousing, this consolidation process is enhanced by the activation of the amygdala (Hamann, 2001; LaBar & Cabeza, 2006; Phelps, 2004; Talmi, 2013). The amygdala coordinates the formation of both negative and positive emotional memories through its interactions with other brain structures and by initiating physiological bodily responses (Cahill & McGaugh, 1998; Dolcos, LaBar & Cabeza, 2005; Hamann, 2001; LaBar & Cabeza, 2006; Talmi, 2013; Weniger, Lange & Irle, 2006). In fact, without the amygdala, the emotional effects of memory are markedly hampered (Hamann, 2001).

The neural mechanisms through which the amygdala coordinates the process of explicit EM formation are complex and multifactorial. The amygdala integrates information from several brain regions through its reciprocal connections with distinct cortical and subcortical brain structures, including the sensory cortex, thalamus, hypothalamus (and, by extension, the HPA

axis), prefrontal cortex (PFC), and the medial temporal lobe (MTL) memory system (i.e., the hippocampus and ento- and perirhinal cortices; LaBar, 2007; LaBar & Cabeza, 2006). The modulatory activity of the amygdala across these various brain structures during explicit EM formation is achieved via neurohormonal activity. For example, in response to an emotional stimulus/event, the adrenal gland releases: (1) glucocorticoids (i.e., cortisol), which readily pass the blood-brain barrier and activate glucocorticoid receptors in the amygdala; and (2) epinephrine, which stimulates vagal afferent neurons (via β-adrenergic receptors) that project to the solitary tract nucleus in the brainstem which, in turn, sends noradrenergic projections to the (basolateral) amygdala (LaBar & Cabeza, 2006; McGaugh, 2000). In response to emotionally-arousing information, enhanced glucocorticoid receptor activation in the amygdala (resulting from the high dose of cortisol released from the adrenal gland), in addition to norepinephrine activity in the basolateral amygdala, is associated with greater memory consolidation (i.e., strengthening of the memory trace; LaBar & Cabeza, 2006, Phelps, 2004). This phenomenon occurs via enhanced glutamatergic synaptic plasticity in the hippocampus that results from: (1) the glutamatergic projections sent from the basolateral amygdala to the hippocampus; and (2) the increased concentration of norepinephrine in the brain (LaBar & Cabeza, 2006; McGaugh, 2000; Tully & Bolshakov, 2010; Yang & Wang, 2017). Indeed, several neuroimaging studies have demonstrated a positive correlation between amygdalar activation during the encoding of emotional information and subsequent memory performance (Dolcos, LaBar & Cabeza, 2005; LaBar & Cabeza, 2006). Interestingly, the neural processes underlying the enhanced formation of emotional memories described above appears dependent upon the stimulus' arousal, not valence (Kensinger & Corkin, 2004). For example, Kensinger and Corkin (2004) scanned HCs using functional magnetic resonance imaging (fMRI) during the encoding and subsequent

retrieval of neutral, arousing negative (e.g., "rape") or non-arousing negative (e.g., "sorrow") words. These researchers found that, as expected, participants remembered more arousing and non-arousing negative words compared to neutral words. Analysis of the fMRI data revealed a significant correlation between the successful encoding of arousing negative words and the activation of the left amygdala and the left hippocampus; however, this same pattern of amygdalar-hippocampal activation was not found during the successful encoding of the non-arousing negative words. Instead, these researchers found a significant correlation between the successful encoding of non-arousing negative words and the activation of the left inferior PFC and the left hippocampus. Kensinger and Corkin (2004) reconciled these findings by suggesting the presence of two distinct neural networks responsible for the processing of arousal and valence during the formation of emotional memories. This research supports the potential mechanism of EM formation described earlier which argues that amygdalar activation is sensitive to emotional arousal, and the amygdalar-hippocampal interaction is essential for the consolidation of emotionally-arousing information.

There is growing evidence in the scientific literature that MDD is associated with structural changes in the hippocampus and amygdala. Numerous reports implicate reduced hippocampal volume as a common feature of MDD (MacQueen & Frodl, 2011; Malykhin et al., 2010; McKinnon et al., 2009; Schmaal et al., 2016). An early meta-analysis of 32 magnetic resonance imaging (MRI) studies confirmed that, compared to HCs, hippocampal volume is indeed reduced in individuals with MDD; however, the extent of hippocampal volume reduction appears to be affected by illness history, with this structural change only observed in patients with an illness duration of at least ~2 years and/or patients who had experienced more than 1 MDE (McKinnon et al., 2009). A more recent meta-analysis provided further support for this

observation, reporting that reduced hippocampal volume in MDD is associated with more than 1 MDE and an age of onset of ≥ 21 (Schmaal et al., 2016). Consensus on the pattern of volumetric amygdalar change observed in MDD is less unified, with some studies reporting an enlarged amygdalar volume in MDD (e.g., Lange & Irle, 2004; Weniger, Lange & Irle, 2006) and others reporting no difference in amygdalar volume in MDD compared to HCs (e.g., Schmaal et al., 2016). A meta-analysis of 13 MRI studies may have identified the reason for these inconsistencies (Hamilton, Siemer & Gotlib, 2008). For example, in their meta-analysis, Hamilton, Siemer and Gotlib (2008) initially found no overall difference between the amygdalar volume of MDD patients and HCs; however, further analyses discovered that, compared to HCs: (1) medicated MDD patients had significantly increased amygdalar volume; and (2) unmedicated MDD patients had significantly reduced amygdalar volume. These observations may be explained as a result of (1) treatment-induced neurogenesis and/or gliogenesis in the amygdala and (2) stress-induced atrophy from glucocorticoid excitotoxicity, respectively (Bowley et al., 2002; Hamilton, Siemer & Gotlib, 2008).

Whether these structural changes reverse or normalize during clinical remission remains an unanswered question. In an MRI study comparing unmedicated acutely depressed MDD participants, unmedicated euthymic MDD participants, and HCs, Caetanoa et al. (2004) found that, although the total group of unmedicated MDD participants did not differ in amygdalar or hippocampal volume compared to HCs, the unmedicated remitted MDD participants had significantly larger hippocampal volume compared to the unmedicated acutely depressed MDD participants, suggesting the potential for increased hippocampal neurogenesis upon clinical remission from depressive symptoms. A longitudinal study by Frodl et al. (2008) found that MDD participants who took antidepressant medication(s) displayed significantly larger left

hippocampal volume three years after their initial baseline assessment compared to those who did not take antidepressant medication(s); however, these researchers found that, overall, clinical remission had no effect on hippocampal or amygdalar volume three years after the initial baseline assessment.

Given the important role both the amygdala and hippocampus play in the formation of emotional memories, volumetric changes associated with these structures in MDD may have a profound effect on explicit EM during both the acute and euthymic stages of the illness. Indeed, a study by Weniger, Lange and Irle (2004) showed that, compared to HCs, medicated MDD participants exhibited: (1) enlarged amygdalar volume; (2) reduced hippocampal volume; and (3) significantly worse performance on an EM paradigm. These findings nicely support previous literature on the neural underpinnings of EM in MDD and their influence on the processing of emotional information. These findings also support a mechanism whereby the cognitive symptoms and emotional processing impairments caused by structural neural changes may persist into euthymia.

While research investigating the cognitive and neural underpinnings of EM in MDD is an active area of research, questions remain about the behavioural patterns of EM in MDD for *specific* sub-domains of cognition (i.e., explicit EM), and how these patterns differ during the acute and euthymic stages of the illness.

Aim of the Current Thesis

The current thesis sought to assess explicit EM performance in MDD during both the acute and euthymic stages of the illness. In Chapter 2, a systematic review of explicit EM in mood disorders during the acute and euthymic illness stages is presented. This review highlights

the paucity of, and need for, future research investigating explicit EM in MDD during euthymia, and recommends methodological considerations for future research investigating explicit EM. Chapter 3 then presents our original work on explicit EM performance in a well-characterized sample of euthymic MDD participants compared to age/sex/gender/IQ-matched HCs. The primary outcome of this study was explicit EM performance (assessed using memory sensitivity, *d'*, indexes) on a one-week delayed incidental recognition memory test. Chapter 4 then introduces and discusses preliminary results from a follow-up study to the original work presented in Chapter 3. The primary goal of this ongoing follow-up study is to assess the influence of psychologically-relevant factors (i.e., self-reported personal relevance and subjective valence categorization of the stimuli) on explicit EM performance in MDD during euthymia. Finally, Chapter 5 includes an integrative discussion of the findings from the work in Chapters 2 through 4, with a focus on the theoretical and clinical implications of our findings, the strengths and limitations of the aggregate research, and future directions.

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CHAPTER 2

Explicit Emotional Memory Biases in Mood Disorders: A Systematic Review

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Manuscript published in: Psychiatry Research

Bogie, B. J. M., Persaud, M. R., Smith, D., Kapczinski, F. P., & Frey, B. N. (2019). Explicit emotional memory biases in mood disorders: A systematic review. *Psychiatry Research, 278*, 162–172. doi: 10.1016/j.psychres.2019.06.003

Abstract

Research suggests that major depressive disorder (MDD) and bipolar disorder (BD) are both associated with unique emotional memory (EM) biases. To better elucidate the EM phenotypes of these disorders, we systematically reviewed the literature on non-autobiographical explicit EM biases in individuals with MDD and BD compared to healthy controls. The following databases were searched: Cochrane, Embase, HAPI, LILACs, Medline, PsycInfo, and Web of Science. Grey literature and hand searches were also performed. Fourteen studies met full eligibility criteria. Eleven studies included data from an MDD sample (10 during acute depression, 1 during euthymia) and 3 studies included data from a BD sample (2 during acute mood episodes, 1 during euthymia). Only 3 of the studies in acute depression revealed a negative explicit EM bias. One study in MDD during euthymia revealed an EM deficit for negative stimuli. One of the two studies in BD (type I; BD-I) during an acute mood episode revealed a positive explicit EM bias, while the other showed no bias. One study in BD during euthymia showed an EM deficit for negative stimuli. Overall, this review concludes that current empirical evidence does not readily support the existence of an explicit EM bias in MDD during acute depression. The identification and implications of potential moderating factors on explicit EM performance in MDD and BD during both illness stages are discussed.

Systematic Review Registration ID: CRD42017069909

Key Words: bipolar disorder, cognition, emotion, major depressive disorder, emotional memory, mood-congruent memory, systematic review

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are chronic, disabling conditions characterized by abnormal changes in mood state (American Psychiatric Association, 2013; Goldstein, 2010). MDD and BD together affect approximately 300 million people worldwide (American Psychiatric Association, 2013; Goldstein, 2010; World Health Organization, 2017). MDD is defined as a disorder consisting of recurrent major depressive episodes, which may include extended periods of low mood and/or loss of pleasure or interest in daily activities, changes in appetite, sleep disturbances, changes in psychomotor activity, feelings of worthlessness, decreased cognitive abilities, and/or suicidal ideation (American Psychiatric Association, 2013). BD is associated with both major depressive episodes and either mania (type I BD; BD-I) or hypomania (type II BD; BD-II; American Psychiatric Association, 2013; Goldstein, 2010). Mania is characterized by heightened or irritable mood with increased self-esteem, decreased sleep, racing thoughts, increased distractibility, increased participation in goal-directed activities, and/or increased participation in potentially harmful activities (American Psychiatric Association, 2013; Goldstein, 2010). Hypomania is characterized by the same symptoms as mania, but the symptoms are typically less severe and, by definition, the hypomanic episodes do not cause marked functional impairment (American Psychiatric Association, 2013).

Disturbances in several cognitive domains have been associated with MDD and BD, including changes in attention, memory, planning, and verbal fluency (Bora and Pantelis, 2015; Marvel and Paradiso, 2004; Rock et al., 2013). A specific cognitive feature suggested to be associated with both disorders is the presence of an emotional memory (EM) bias. The conceptualization of an EM bias in existing literature is ambiguous. In this systematic review, we

operationally define an EM bias as the tendency for individuals with MDD and BD to *more* accurately remember information of a particular valence (i.e., positive or negative) compared against healthy controls (HCs; LaBar and Cabeza, 2006; LaBar and Phelps, 1998). On the other hand, the tendency for individuals with MDD and BD to *less* accurately remember information of a particular valence (i.e., positive or negative) compared against HCs is characterized here as an EM deficit. In this way, EM performance in HCs represents the behavioural phenotype expected under normal physiological conditions and therefore represents an estimate of baseline performance to which performance in the clinical groups can be compared. Previous studies have consistently shown that HCs display more accurate memory for both emotionally-positive and emotionally-negative information, compared to emotionally-neutral information (Asl et al., 2015; Cahill and McGaugh, 1995; Flaisch et al., 2016; Williams et al., 2015). This may be explained by the observation that emotional salience is more likely to signify an event that is relevant to survival (Cahill and McGaugh, 1995; Flaisch et al., 2016). It is thus conceivable that enhanced memory for emotional stimuli (positive and negative) is an evolved adaptation to promote human survival (Hamann, 2001). Cognitive neuroscience research has implicated the amygdala as a key player in the formation of emotional memories (LaBar and Cabeza, 2006; LaBar and Phelps, 1998; LeDoux, 1993). It is widely believed that, upon exposure to emotionally-arousing stimuli, increased activation of the amygdala leads to the modulation of visual cortex, prefrontal cortex, and hippocampal activity through the recruitment of stress hormones (i.e., norepinephrine) and corticosteroids (Hamann, 2001; Kensinger and Corkin, 2004; LaBar and Cabeza, 2006; Turkileri and Sakaki, 2017). This modulatory interaction between the amygdala and other brain regions critical for memory formation consequently results in more efficient memory encoding and retrieval for emotional information. Despite this, research supports the existence of unique EM

biases in individuals diagnosed with a mood disorder, such as MDD and BD (Leppänen, 2006). Therefore, there may be a malfunction in this evolved adaptation in mood disorders that is responsible for manifesting unique EM biases, or the lack thereof (Durisko et al., 2016; Wakefield, 1992).

Considerable research has explored the existence of a mood-congruent negative EM bias in depression (Matt et al., 1992; Watkins et al., 1992; Wittekind et al., 2014). A mood-congruent bias refers to the more accurate memory retrieval of information consistent with one's current emotional state (Moritz et al., 2005). Several theories have hypothesized that depressed individuals show a proclivity towards remembering negative emotional stimuli (Beck, 1979; Bower, 1981; Matt et al., 1992; Williams et al., 1988). For example, the cognitive model of depression, which has been informed by decades of clinical, cognitive, biological, and evolutionary research (e.g., Beck, 1974, 2008; Beck and Bredemeier, 2016), posits that individuals suffering from depression may experience a systemic negative cognitive bias across all levels of information processing, including emotional reactivity and memory (Beck and Bredemeier, 2016). When exposed to a stressor, cognitive structures, called *schemas*, within which beliefs are set, become differentially activated depending on the stimulus' intensity. In depression, a triad of unique maladaptive cognitive schemas exist, collectively termed the cognitive triad, that may lead to negative beliefs about the self, world, and future in response to a negative stimulus (Beck, 1974, 2008; Beck and Bredemeier, 2016). These schemas, in turn, may enforce negative information processing biases and reinforce the symptoms of depression through negative subjective appraisals. For instance, negative subjective appraisals can lead to: (1) automatic negative thoughts, which are responsible for the cognitive symptoms of MDD; and/or (2) activation of the autonomic nervous system and immune system (also mediated by the

neurotransmission of serotonin and dopamine), which results in the "sickness behaviours" observed in MDD (i.e., anhedonia, loss of energy, etc.; Beck and Bredemeier, 2016). In MDD, and conceivably in mood disorders in general (see Panchal et al., 2019), this cognitive mechanism is hypothesized to underly symptoms of an acute mood episode and promote biased interpretations of the self and environment. As such, the phenomenon of EM may play a clinically-relevant role in the manifestation and maintenance of the symptoms associated with MDD and BD. Consistent with this model, Matt et al. (1992) reported that acutely depressed individuals display a mood-congruent negative EM bias. However, recent evidence has challenged the notion that such a mood-congruent bias exists in MDD (Bylsma et al., 2008; Cheng et al., 2015). Furthermore, while research into cognitive deficits in BD has increased in recent years (see Lima et al., 2017), questions remain about the existence of a mood-congruent EM bias in BD.

To enhance our understanding of the cognitive deficits associated with mood disorders, the current paper systematically reviewed the literature to investigate the existence of a non-autobiographical explicit EM bias in individuals with MDD and BD. Considering the similar clinical and cognitive aspects of these mood disorders (Cuellar et al., 2005), researchers have identified a necessity for a comprehensive joint evaluation of the cognitive phenotypes associated with MDD and BD (Bearden et al., 2006; MacQueen and Memedovich, 2017). The current investigation involved the assessment of incidental, rather than intentional, emotional memories. Incidental memories refer to "memories that are acquired without intention" (i.e., without attention, effort or resources; Glisky, 2011) and represent a more prominent phenotype in daily functioning (Kontaxopoulou et al., 2017). Patterns of incidental EM formation thus inform a more naturalistic understanding of EM biases in mood disorders by highlighting

cognitive processes that function independently from one's conscious attention. Explicit EM was chosen as the focus for the current review because it refers to the classification of EM that involves conscious recollection of information (Hine and Tsushima, 2018). Moreover, research investigating explicit EM involves experimental procedures with highly controlled stimulus sets and memory tasks (i.e., compared to other sub-domains of memory that involve the retrieval of personal experiences or self-generated material; Matt et al., 1992).[1] We classified EM differences in MDD and BD according to: (1) individuals experiencing a current mood episode compared to HCs; and (2) euthymic individuals compared to HCs.

Methods

Complete methodology for the current systematic review was registered in PROSPERO (Bogie et al., 2017), an international prospective register of systematic reviews.

Search strategy

The current review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A literature search was performed to retrieve peer-reviewed, primary studies with a population diagnosed with MDD or BD.

A research librarian (D.S.) constructed the search strategy. The librarian combined subject headings and keywords to build a literature search comprised of three concepts: 'emotional memory bias', 'major depressive disorder', and 'bipolar disorder'. 'Emotional memory' is not an established term in the indexing of health literature. Consequently, the current

[1]The reader is directed to Gaddy and Ingram (2014) and Köhler et al. (2015) for a review of implicit and autobiographical memory in MDD, respectively.

search strategy was necessarily and purposely broad in scope to accommodate for variations in terminology related to the concept of EM (see Supplementary File 1). The search strategy is also available on PROSPERO (Bogie et al., 2017).

The following databases were searched on December 10, 2018: Cochrane, OVID Medline, OVID Embase, OVID PsycInfo, OVID Health and Psychosocial Instruments, LILACs, and Web of Science. A search for grey literature and hand searches were also performed. While previous reviews/meta-analyses exist that investigate emotional information processing phenotypes in depression or BD *in general* (e.g., Leppänen, 2006; Matt et al., 1992; Robinson et al., 2006; Vöhringer et al., 2013), no systematic review has focused on non-autobiographical explicit EM biases in MDD and BD *specifically*. Therefore, no geographic, language, or date restrictions were imposed in the current review. The search strategy was peer-reviewed by a second librarian. The reference management software RefWorks (2018) was used to organize retrieved literature from all searches and to detect duplicate citations.

Identification of eligible studies

Sources were eligible if they included original data from subjects diagnosed with MDD or BD, aged 18 to 66, compared against an HC group. To be eligible, diagnoses of MDD or BD must have been confirmed using standardized, validated diagnostic assessment tools that adhered to either the Diagnostic and Statistical Manual of Mental Disorders' (DSM; American Psychiatric Association, 2013) or the International Classification of Diseases' (ICD; World Health Organization, 2018) criteria for MDD and BD. Studies were eligible if they measured non-autobiographical explicit EM performance using any type of non-autobiographical explicit EM task that included experimentally-controlled positive, neutral and/or negative stimuli.

Studies including data from mixed populations were eligible if the data were reported separately for MDD and BD samples.

Studies were ineligible if they included subjects with MDD or BD with a co-morbid diagnosis of delusional disorder, schizoaffective disorder, schizophrenia, and/or current alcohol or substance use disorder. Studies were excluded if the study design involved an intervention before the assessment of EM, or if subjects were privy to the memory task.

One author (D.S.) performed database and grey literature searches and two authors (B.J.M.B., M.R.P.) independently performed hand searches. Two authors (B.J.M.B., M.R.P.) independently reviewed all titles and abstracts for pre-defined eligibility criteria. Disagreement was resolved through discussion. Potentially eligible studies were read in full independently by two authors (B.J.M.B., M.R.P.) to confirm eligibility. Disagreement was resolved through discussion.

Data extraction

Data on study methodology, sample composition and study findings, were extracted from eligible studies and recorded in a data extraction spreadsheet independently by two authors (B.J.M.B., M.R.P.). Discrepancies were resolved through discussion.

Quality assessment of eligible studies

The quality of eligible studies was assessed using a revised form of the Effective Public Health Practice Project's (EPHPP) quality assessment tool for quantitative studies (Effective Public Health Practice Project, 1998). This validated tool includes six components: selection bias; design; confounders; blinding; data collection methods; and withdrawals and dropouts. The revised EPHPP tool used here disregarded sections B and D (Q1) because they were irrelevant to

the types of studies included in the current review. Each component was assigned a rating of weak, moderate or strong. All component ratings contributed to a global rating. The procedure for converting the component ratings into a global rating has been reported elsewhere (Hall et al., 2017). Two authors (B.J.M.B., M.R.P.) independently assessed the quality of each eligible study. Disagreement was resolved through discussion.

Results

Given the necessary breadth of our search strategy, our searches yielded 43,883 titles. Following the PRISMA guidelines (Moher et al., 2009), title screening excluded 42,128 articles and abstract screening excluded a further 1,014 articles. The remaining 741 articles underwent full text review. Of these, 14 studies met full eligibility criteria. The remaining 723 articles were excluded primarily because of insufficient diagnostic procedures (e.g., the use of inappropriate diagnostic tools, not assessing co-morbid diagnoses) and exclusionary methodological designs (e.g., interventional studies that imposed an intervention before the assessment of EM). Figure 2.1. summarizes the results of each step in the screening process.

Of the 14 eligible articles, 11 included an MDD sample and 3 included a BD sample (see Table 2.1. for a summary of the included studies). Seven of the included studies received a strong global quality rating (Baños et al., 2001; Hamilton and Gotlib, 2008; Kauer-Sant'Anna et al., 2008; Olsen et al., 2015; Ridout et al., 2009; Whalley et al., 2009; Williams et al., 2015), five received a moderate rating (Delgado and Chaves, 2013; Denny and Hunt, 1992; Ellwart et al., 2003; Gotlib et al., 2004; Liu et al., 2012) and two received a weak rating (Rinck and Becker, 2005; Serfaty et al., 2002) according to the EPHPP quality assessment tool. The eligible studies assessed explicit EM in samples of: (1) MDD, acutely depressed (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Gotlib et al., 2004; Hamilton and Gotlib, 2008; Liu et al., 2012;

Figure 2.1. PRISMA flow diagram summarizing the results of the screening process (Moher et al., 2009).

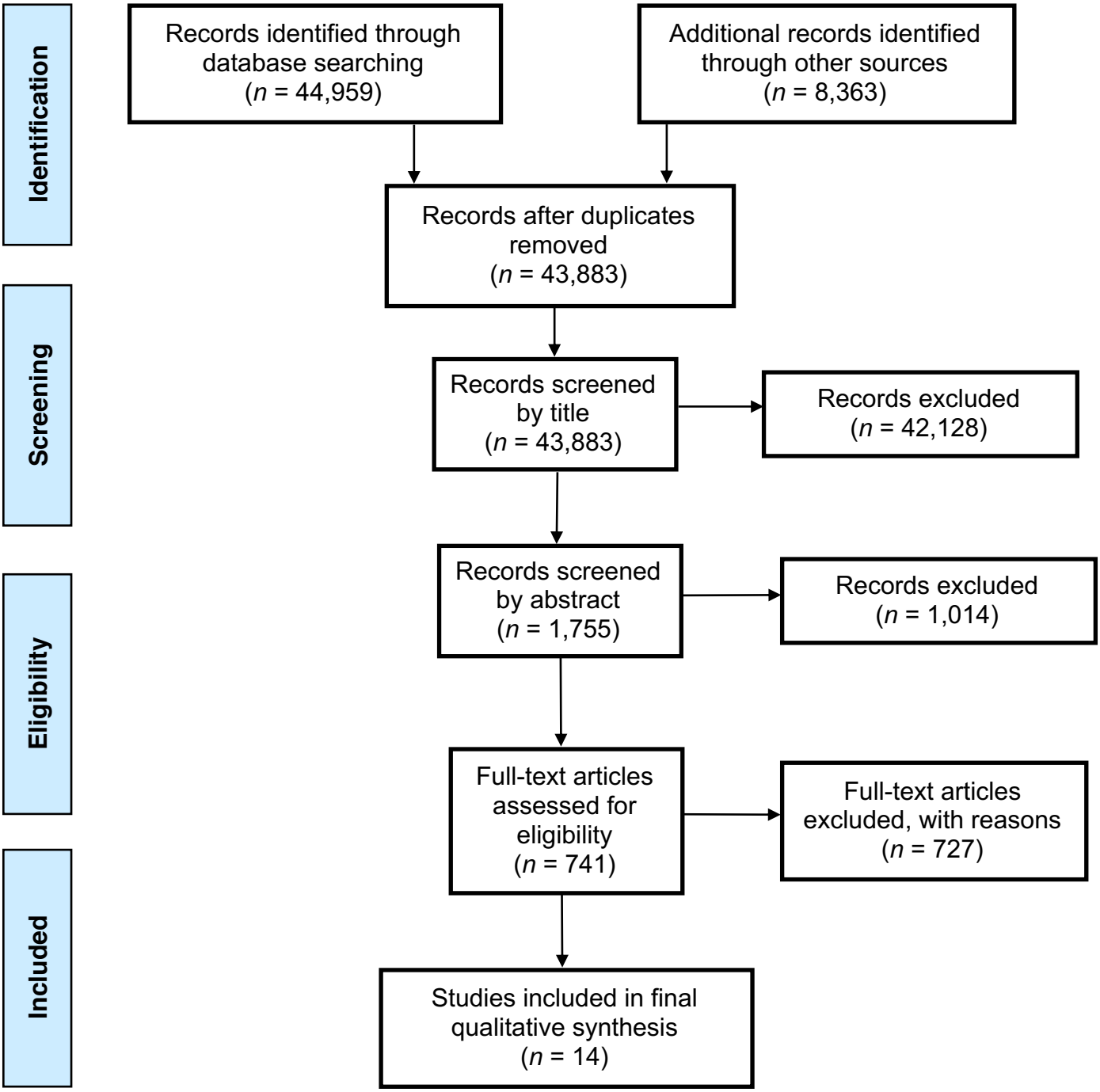

Table 2.1. Summary of included articles.

Study	Groups (Sample Size, % Female, Mean Age)	Memory Task(s)	Stimuli and Valences	Summary of Findings
Baños et al. (2001)	MDD, acute depression (n = 20, 75%, age range: 20-50) HC (n = 20, 80%, age range: 20-50) (Panic disorder sample also included)	Graphemic, semantic, and self-referent encoding tasks; completed two distractor tasks and an IM task; completed free recall explicit EM task	Words; positive, neutral, depression-related (i.e., negative)	No significant between-group differences on EM; significantly more depression-related words were recalled within each group ($p < 0.001$); significantly better EM for neutral words within both MDD and HC groups following self-referent encoding ($p < 0.001$)
Delgado and Chaves (2013)	BD-I psychotic, manic episode (n = 19, 63.2%, 37.3) BD-I nonpsychotic, manic episode (n = 12, 50%, 47.0) HC (n = 27, 74.1%, 39.2)	Word span task: word lists of the three valence categories were consecutively presented; immediate recall paradigm	Words; positive, neutral, negative	Significant between-group difference for the recall of positive words ($p = 0.042$); BD-I nonpsychotic > BD-I psychotic > HCs
Denny and Hunt (1992)	MDD, acute depression (n = 16, 100%, 29.2) HC (n = 16, 100%, 24.0)	Self-referent encoding task; immediately completed IM and explicit EM tasks in counterbalanced order (explicit EM task was free recall)	Words; positive, negative	The MDD group recalled significantly fewer words overall ($p < 0.001$); the MDD group recalled significantly fewer positive words than HCs ($p < 0.001$); the MDD group recalled significantly more negative than positive words ($p < 0.001$); HCs

				recalled significantly more positive than negative words ($p < 0.01$)
Ellwart et al. (2003)	MDD, acute depression (n = 36, 77.8%, 42.1) HC (n = 36, 72.2%, 42.5)	Self-referent encoding task; immediately completed IM and explicit EM tasks in counterbalanced order (explicit EM task was free recall)	Words; positive, neutral, depression-related (i.e., negative)	No significant between-group differences; both MDD and HC groups recalled significantly more positive words ($p < 0.05$)
Gotlib et al. (2004)	MDD, acute depression (n = 88, 70.7%, 34.5) HC (n = 55, 75.0%, 33.6) (Social phobia sample also included)	Self-referent encoding task; three-minute delay/filler task; completed EM free recall task	Words; positive, depression-related (i.e., negative)	The MDD group recalled significantly more depression-related words than HCs ($p < 0.05$); both MDD and HC groups recalled significantly more positive words ($p < 0.01$)
Hamilton and Gotlib (2008)	MDD, acute depression (n = 14, 57%, 36.5) HC (n = 12, 50%, 31.4)	Participants rated the emotional intensity and affective valence of 210 images (70 in each valence category) while in an fMRI scanner; returned one week later for incidental recognition EM task	IAPS images; positive, neutral, negative	The MDD group had significantly greater memory sensitivity for negative images than HCs ($p < 0.05$); HCs recalled significantly more positive than negative images ($p < 0.05$)
Kauer-Sant'Anna et al. (2008)	Emotional and neutral conditions; BD groups comprised types I and II Euthymic BD-Emotional (n = 10, 83%, 45.7)	Participants viewed an 11-slide slideshow; conditions differed in slides 5-8 (phase 2); immediate emotional intensity rating; one-week delay; incidental recognition EM task (multiple-choice test)	Narrated slide show; emotional (negative) and neutral conditions	The BD group displayed significantly worse memory performance overall compared to HCs ($p = 0.002$); the BD group displayed significantly worse memory for the negative material compared to HCs

	Euthymic BD-Neutral (n = 10, 67%, 43.2) HC-Emotional (n = 10, 75%, 42.4) HC-Neutral (n = 10, 75%, 43.5)			(p = 0.01); no significant difference between BD-Emotional and BD-Neutral groups on negative EM performance; the HC-Emotional group had significantly greater memory performance than the HC-Neutral group for the negative information (p = 0.008)
Liu et al. (2012)	MDD, acute depression (n = 71, 47.9%, 27.3) HC (n = 61, 49.2%, 26.1)	Participants rated each word on a pleasant/arousal scale; no delay/filler task; immediate EM tasks (free recall and recognition tasks)	Words; positive high-arousal, positive low-arousal, neutral, negative high-arousal, negative low-arousal	The MDD group recalled significantly fewer positive high- and low-arousal, neutral, and negative high-arousal words than HCs (all ps < 0.001); both groups recalled significantly more high-arousal than low-arousal words (p < 0.05); HCs recalled significantly more positive high-arousal than negative low-arousal words (p < 0.001); no significant differences for the recognition task
Olsen et al. (2015)	MDD, acute depression (n = 18, 100%, 35.9, age range: 18-55) HC (n = 33, 100%, 38.4, age range: 18-58)	Participants rated the emotional intensity of 90 images (30 in each valence category); returned one day later for incidental recognition EM task	IAPS images; positive, neutral, negative	No significant between-group differences; all groups recognized negative images more accurately than positive images (p < 0.05)

	(Schizophrenia sample also included)			
Ridout et al. (2009)	MDD, acute depression (n = 16, 68.8%, 43.7) HC (n = 18, 77.8%, 39.3)	Participants completed a gender identification task for 30 images of human faces; five-minute filled delay; completed incidental recognition EM task	Images of human faces; happy (i.e., positive), neutral, sad (i.e., negative)	The MDD group performed significant worse on the EM task overall compared to HCs ($p < 0.001$); no significant difference between the MDD and HC groups on EM performance
Rinck and Becker (2005)	MDD, acute depression (n = 27, 100%, 23.5) HC (n = 55, 100%, 21.4) (Social phobia sample also included)	Encoding tasks included searching for words one-by-one in a word matrix and self-referent encoding; average of one day between matrix and self-referent tasks; additional five-minute delay/filler task after self-referent encoding; completed IM and explicit EM (free recall) tasks in counterbalanced order, separated by a five-minute distracter task	Words; positive, neutral, depression-related (i.e., negative)	The MDD group recalled significantly more depression-related words than the HC group (F = 5.15); the MDD group recalled significantly more depression-related words than positive words, and significantly more positive than neutral words (F = 4.91); HCs recalled significantly more positive words than any other valence (F = 5.39)
Serfaty et al. (2002)	MDD, acute depression (n = 15, 33.3%, 41.7) HC (n = 15, 46.7%, 33.3)	Self-referent encoding task; no delay/filler task; immediate EM task (free recall), five-minute delay, and recognition task	Words; positive, neutral, negative	The MDD group recalled significantly fewer positive ($p < 0.002$) and negative ($p < 0.001$) words than HCs; both groups recalled significantly more positive than negative words ($p < 0.002$ for HCs, $p < 0.02$ for MDD);

				no significant between-group differences for recognition EM; both groups recognized significantly more positive than negative words ($p < 0.002$)
Whalley et al. (2009)	BD (included euthymic, acute manic, and acute depressed, with and without psychotic features; $n = 14$, 35.7%, 41.5) HC ($n = 14$, 28.6%, 31.4) (Schizophrenia sample also included)	Participants rated the emotional intensity of 72 images (36 in each valence category) while in an fMRI scanner; the incidental recognition EM task occurred immediately after the scan	IAPS images; positive, neutral	No significant between-group differences; both MDD and HC groups recognized significantly more positive than neutral images ($p = 0.01$)
Williams et al. (2015)	Pregnant and non-pregnant conditions. Euthymic MDD-Pregnant ($n = 14$, 100%, 31.0) Euthymic MDD-Non-pregnant ($n = 13$, 100%, 27.0) HC-Pregnant ($n = 30$, 100%, 29.0) HC-Non-pregnant ($n = 20$, 100%, 23.0)	Participants rated the emotional intensity of 144 images (48 in each valence category); one-week delay; completed incidental recognition memory test	IAPS images; positive, neutral, negative	Pregnancy status did not significantly affect memory performance; participants with a history of MDD had significantly worse recognition memory for negative images compared to HCs ($p = 0.01$); there was no significant difference in EM performance between pregnant women with and without a history of MDD

BD, bipolar disorder; EM, emotional memory; fMRI, functional magnetic resonance imaging; HC, healthy control; IAPS, International Affective Picture System (Lang et al., 1997); IM, implicit memory; MDD, major depressive disorder

Note: The words "recalled" and "recognized" were carefully chosen in the final column of this table to denote findings from free recall and recognition memory paradigms, respectively.

Olsen et al., 2015; Ridout et al., 2009; Rinck and Becker, 2005; Serfaty et al., 2002); (2) MDD, euthymic (Williams et al., 2015); (3) BD, acute mood episode (Delgado and Chaves, 2013; Whalley et al., 2009); and (4) BD, euthymic (Kauer-Sant'Anna et al., 2008). Findings from the included studies are organized below according to the included sample's episode status and the type of explicit EM paradigm used (i.e., free recall versus recognition tasks). Previous research has identified partly distinct *and* partly shared neural correlates underlying explicit recall and explicit recognition memory processes, making both paradigms appropriate at assessing explicit EM (Buckner and Koutstaal, 1998; Cabeza and Nyberg; 2000). For the purposes of this review, stimuli originally defined as "happy" were recategorized as positive and stimuli originally defined as "depression-related" or "sad" were recategorized as negative; analyses of any additional valences other than positive, neutral and negative are not discussed (e.g., panic-related [Baños et al., 2001], physically- and socially-threatening [Gotlib et al., 2004], social phobia-related [Rinck and Becker, 2005] stimuli). These stimuli were largely included to assess explicit EM in other groups included in these studies (i.e., panic disorder [Baños et al., 2001] and social phobia [Gotlib et al, 2004; Rinck and Becker, 2005] groups). Methodological heterogeneity across the included studies precluded meta-analysis. For example, there was significant heterogeneity across included studies regarding the study design, use of encoding task, type of stimuli, valences of stimuli, delay period, memory task, and the nature of the dependent variable (i.e., percent correct, memory sensitivity, normalized memory scores). Therefore, given this diversity, the authors did not find it meaningful or appropriate to conduct a meta-analysis (see also Hasselbalch et al. [2011] for similar reasoning regarding the decision to perform a meta-analysis).

Explicit emotional memory in major depressive disorder during acute depression

A total of 10 studies assessed explicit EM in currently depressed individuals with MDD (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Gotlib et al., 2004; Hamilton and Gotlib, 2008; Liu et al., 2012; Olsen et al., 2015; Ridout et al., 2009; Rinck and Becker, 2005; Serfaty et al., 2002). Of these 10 studies, 7 studies (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Gotlib et al., 2004; Liu et al., 2012; Rinck and Becker, 2005; Serfaty et al., 2002) used a free recall paradigm and 5 studies (Hamilton and Gotlib, 2008; Liu et al., 2012; Olsen et al., 2015; Ridout et al., 2009; Serfaty et al., 2002) used a recognition memory paradigm. Results within this section are reported separately according to free recall and recognition paradigms to account for variations in study protocol. It should be noted that 3 of the included studies in this section used exclusively female subjects (Denny and Hunt, 1992; Olsen et al., 2015; Rinck and Becker, 2005). Most of the included studies with an acutely depressed MDD sample recruited subjects from specialized outpatient clinics (Baños et al., 2001; Gotlib et al., 2004; Hamilton and Gotlib, 2008; Liu et al., 2012; Olsen et al., 2015; Ridout et al., 2009; Serfaty et al., 2002), while the remaining studies recruited subjects from inpatient units (Denny and Hunt, 1992; Ellwart et al., 2003), or community samples (Olsen et al., 2015; Rinck and Becker, 2005).

Only 2 of the 7 studies investigating explicit EM using a free recall paradigm found an explicit EM bias in MDD (Gotlib et al., 2004; Rinck and Becker, 2005), a finding that does not support an explicit EM bias during acute MDD (it is noted, however, that Denny and Hunt [1992] showed that, within the MDD group, negative stimuli were recalled significantly more accurately than positive stimuli). These 2 studies found that the MDD group recalled more negative stimuli than HCs. Three of the remaining 7 studies found an EM deficit in the MDD

group compared to HCs. For example, Denny and Hunt (1992) found that the MDD group recalled significantly fewer positive stimuli than HCs; Serfaty et al. (2002) found that the MDD group recalled significantly fewer positive and negative stimuli than HCs; and Liu et al. (2012) found that the MDD group performed significantly worse than HCs on all but one valence category (the negative low-arousal category, where there was no between-group difference). While these results may reflect an EM deficit *specifically*, it is possible that these results reflect a rather *general* memory impairment in MDD. For example, Denny and Hunt (1992) and Serfaty et al. (2002) both showed that the MDD groups had worse overall memory compared to HCs, and Liu et al. (2012) showed that the MDD group had significantly worse memory for neutral stimuli compared to HCs, which is indicative of a general memory impairment.

Of the 5 studies (Hamilton and Gotlib, 2008; Liu et al., 2012; Olsen et al., 2015; Ridout et al., 2009; Serfaty et al., 2002) that used a recognition memory paradigm, only the study by Hamilton and Gotlib (2008) demonstrated a negative EM bias in MDD. Furthermore, the study by Ridout et al. (2009) did find a general EM impairment in the MDD group compared to HCs; however, this did not translate into an explicit EM bias or deficit. The remaining studies reported no differences between groups on the explicit EM recognition task.

In summary, neither the free recall nor the recognition memory findings readily support the existence of an explicit EM bias in acutely depressed MDD subjects. The inconsistent findings across included studies assessing explicit EM in acutely depressed MDD subjects may, in part, be explained by important moderating factors (discussed below).

Explicit emotional memory in major depressive disorder during euthymia

Only 1 study assessed explicit EM in a euthymic MDD sample (Williams et al., 2015). Subjects were pregnant and non-pregnant women with a history of MDD compared against

pregnant and non-pregnant HCs. This study employed a recognition memory paradigm using stimuli from the International Affective Picture System (IAPS; Lang et al., 1997). The euthymic MDD females were recruited from specialized outpatient clinical services and community services. This study found that euthymic women with a history of MDD showed significantly worse memory for negative images (i.e., a negative EM deficit) compared to euthymic women without a history of MDD. There were no group differences for positive or neutral images, and pregnancy had no effect on these results.

Explicit emotional memory in bipolar disorder during an acute mood episode

One study compared explicit EM in acutely manic BD-I individuals, with and without psychotic features, against HCs (Delgado and Chaves, 2013). This study employed a verbal episodic memory test using a word span task with an immediate free recall paradigm. All patients in this study were recruited from a psychiatric inpatient unit. This study showed significant group differences on the recall of positive words: the BD-I nonpsychotic group had greater accuracy than the BD-I psychotic group, who in turn had greater accuracy than the HC group on their recall of positive words. Therefore, this study suggests a possible positive EM bias in acute mania.

Another study combined BD-I individuals with acute depression, acute mania, and euthymic individuals (more than half of the BD sample was in an acute mood episode), compared to HCs (Whalley et al., 2009). This study employed a recognition memory paradigm using stimuli from the IAPS (Lang et al., 1997). Patients were recruited from inpatient and outpatient clinics. While both the BD and HC groups recognized significantly more positive images than neutral images (negative images were not included), there was no between-group difference on explicit EM performance.

Explicit emotional memory in bipolar disorder during euthymia

Only 1 study assessed explicit EM in euthymic individuals in a group of BD-I and BD-II subjects (Kauer-Sant'Anna et al., 2008). This study employed a recognition memory paradigm using a narrated slideshow with emotional (negative) and neutral content. The euthymic BD subjects were recruited from a specialized outpatient clinic. The euthymic BD subjects showed significantly worse memory for the emotionally-negative content compared to HCs (i.e., a negative EM deficit); however, these researchers also showed that the BD group demonstrated a general EM impairment compared to HCs. Thus, at present, it is unclear whether these findings represent a general or valence-specific EM deficit for negative information in BD during euthymia.

Discussion

The current systematic review assessed explicit EM in MDD and BD during acute mood episodes and euthymia. The main finding is that the results from the included studies do not readily support the existence of an explicit EM bias in acutely depressed individuals with MDD. In BD, given the low number of included studies, we can only show preliminary evidence for a potential positive EM bias in acute mania (no studies in the current review investigated explicit EM in BD during acute depression); however, future research is needed to replicate this preliminary finding. Similarly, the current review shows preliminary evidence that euthymic individuals with a history of MDD, BD-I, or BD-II do not display an explicit EM bias; instead, preliminary findings suggest the potential for an explicit EM *deficit* for negative stimuli in MDD, BD-I and BD-II during euthymia.

The majority of studies that assessed explicit EM in acutely depressed MDD subjects did not show an explicit EM bias in MDD compared against HCs. Careful consideration of the

methodological nuances revealed a striking similarity across the 7 studies that did not find an explicit EM bias: the delay period between the encoding and memory retrieval tasks was very short, ranging from minutes (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Liu et al., 2012; Ridout et al., 2009; Serfaty et al., 2002) to one day (Olsen et al., 2015). On the other hand, the studies that demonstrated an explicit EM bias in MDD used delay periods ranging from one day (Gotlib et al., 2004; Rinck and Becker, 2005) to one week (Hamilton and Gotlib, 2008), which suggests that less than a day might be too short of a delay to detect potential explicit EM biases in MDD. Indeed, previous research has argued that the beneficial effects of emotionally-arousing stimuli on the mechanisms of EM formation are greater with a longer delay between encoding and memory retrieval tasks (LaBar and Cabeza, 2006). This observation raises the question of what the shortest delay period between encoding and memory retrieval tasks is for an explicit EM bias to be reliably detected. Moreover, is there an interplay between memory paradigm and delay period? The 5 studies (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Liu et al., 2012; Serfaty et al., 2002) that employed a free recall paradigm and found negative results all included a particularly short delay period (minutes), while the 2 studies that found an explicit EM bias (Gotlib et al., 2004; Rinck and Becker, 2005) both included a longer delay period (one day). Similarly, the 4 studies that used a recognition paradigm and found negative results again used a short delay period of minutes (Liu et al., 2012; Ridout et al., 2009; Serfaty et al., 2002) to one day (Olsen et al., 2015), while the one study reporting an explicit EM bias used a delay period of one week (Hamilton and Gotlib, 2008). Hamilton and Gotlib (2008) imposed a one-week delay between encoding and recognition tasks and identified a negative EM bias in MDD during acute depression. Olsen et al. (2015) used a similar methodology to Hamilton and Gotlib (2008); however, these researchers imposed a one-day delay period and

subsequently did not find an explicit EM bias. Again, this observation suggests that a longer delay period may be necessary for detecting an explicit EM bias in MDD. This requirement likely reflects the importance of the time-dependent process of consolidation on the strengthening of the memory trace (Hamann, 2001). Indeed, research suggests that, in response to an emotionally-arousing stimulus, the modulatory activity of the amygdala—through the activation of glucocorticoid receptors and the activity of norepinephrine—leads to glutamatergic synaptic plasticity in the hippocampus (i.e., a time-dependent process; LaBar and Cabeza, 2006; Phelps, 2004). This, in turn, results in enhanced consolidation of the memory trace and, by extension, more accurate memory performance for emotional compared to unemotional stimuli (LaBar and Cabeza, 2006). A longer delay period between the encoding and memory retrieval tasks thus allows more time for the process of glutamatergic synaptic plasticity to translate into enhanced (detectable) EM performance (LaBar and Cabeza, 2006; Phelps, 2004). Therefore, in future studies, we recommend that the minimum delay periods used to investigate an explicit EM bias using free recall and recognition memory paradigms should be at least one day and one week, respectively.

It is also important to consider the potential effects of stimulus type and encoding procedure on explicit EM performance. Five of the 7 studies reporting negative results in an acutely depressed MDD sample used word stimuli (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Liu et al., 2012; Serfaty et al., 2002), while the remaining studies used human faces (Ridout et al., 2009) and IAPS images (Olsen et al., 2015). The 3 studies showing an explicit EM bias in MDD used words (Gotlib et al., 2004; Rinck and Becker, 2005) and IAPS images (Hamilton and Gotlib, 2008); thus, stimulus type alone does not appear to influence explicit EM performance in this population.

Could the lack of an explicit EM bias in acutely depressed MDD subjects be explained by self-referent encoding effects? Evidence suggests that personally-relevant stimuli can profoundly affect memory performance (Abraham, 2013; Zupan et al., 2017). Of the 10 studies including an acutely depressed MDD sample, 6 studies (Baños et al., 2001; Denny and Hunt, 1992; Ellwart et al., 2003; Gotlib et al., 2004; Rinck and Becker, 2005; Serfaty et al., 2002) involved self-referential encoding (i.e., an encoding strategy where information is processed/encoded with reference to the self; Durbin et al., 2017; Zupan et al., 2017). Two of these studies identified a negative EM bias (Gotlib et al., 2004; Rinck and Becker, 2005), while one study (Denny and Hunt, 1992) found that the MDD group performed worse than HCs in the remembering of positive information, and another study (Serfaty et al., 2002) found that the MDD group performed worse than HCs in the remembering of positive and negative information. Future research is therefore needed to better elucidate the influence of personally-relevant stimuli and self-referential encoding on explicit EM performance in individuals with MDD.

The lack of an identified explicit EM bias in acutely depressed MDD subjects may also be understood by considering variability in clinical factors across studies that may have differentially influenced explicit EM performance, such as symptom severity, length of illness, number of previous mood episodes, and medication status. While the present review imposed strict eligibility criteria to control for as many confounding clinical factors as possible (i.e., the use of standardized diagnostic interviews, exclusion of current alcohol and substance use disorders), the impact of the abovementioned variables on explicit EM cannot be discounted. Depressive symptom severity does not seem to influence the overall results of our systematic review since the studies that found an explicit EM bias included subjects with moderately severe depression (Hamilton and Gotlib, 2008) and very severe depression (Gotlib et al., 2004), while

the studies reporting no EM bias included subjects with mild/moderately severe (Liu et al., 2012; Olsen et al., 2015) to severe (Baños et al., 2001; Ridout et al., 2009; Serfaty et al., 2002) depression. However, the influence of illness duration, the number of previous depressive episodes and medication status might also be important factors to consider when assessing explicit EM. Unfortunately, only half of the included studies assessing explicit EM in currently depressed MDD subjects reported information on medication status (Ellwart et al., 2003; Hamilton and Gotlib, 2008; Olsen et al., 2015; Ridout et al., 2009; Serfaty et al., 2002), only 2 studies reported average illness length (Hamilton and Gotlib, 2008; Liu et al., 2012), and no studies reported the number of previous depressive episodes.

Two studies assessed explicit EM in BD subjects during an acute mood episode. Delgado and Chaves (2013) identified a positive EM bias and Whalley et al. (2009) found no explicit EM bias. It should be noted, however, that the study by Whalley et al. combined acutely depressed, acutely manic, and subjects in euthymia into a single BD sample. This is a methodological problem since the grouping of subjects with different mood episode statuses into a single BD group likely confounded the results. For example, given the profound effect of mood state on memory performance (Bower, 1981; Matt et al., 1992), combining participants with different mood states (i.e., mania, hypomania, depression, euthymia) neglects the unique cognitive features of the independent mood states, leading to the potentially inaccurate conclusion of no explicit EM bias. Still, this study reported a bias within the BD group towards remembering positive stimuli with greater accuracy. Given the sample composition of Whalley et al.'s study, and considering that both included studies on BD during an acute mood episode only included BD-I subjects, future research is necessary to differentiate the explicit EM phenotypes of individuals with BD-I from BD-II during an acute depressive or (hypo)manic episode.

Nevertheless, these findings provide preliminary support for a potential positive explicit EM bias in BD-I during an acute mood episode.

Strengths and limitations

This is the first article to comprehensively and systematically review the literature on explicit EM biases in MDD and BD. While previous reviews and meta-analyses have attempted to identify cognitive dysfunction in MDD and BD *in general* (Robinson et al., 2006; Rock et al., 2013; Vöhringer et al., 2013), none have investigated explicit EM *specifically*. Moreover, this review presents and discuses several potential moderating variables that may influence explicit EM performance across MDD and BD during both illness stages. This discussion may inspire several future research foci in the investigation of explicit EM in MDD and BD across illness stages. Despite these strengths, some limitations must be considered. First, there were considerable differences in the sample sizes of included studies. Second, there was an unequal balance of studies including MDD and BD samples (11 versus 3, respectively). As a result, less synthesis was possible in the BD results. Third, only 1 study in each population included a euthymic sample, highlighting the need for more investigation into potential interepisodic explicit EM biases in MDD and BD. Fourth, several studies identified a general memory impairment in the clinical groups compared to the HC group (e.g., Denny and Hunt, 1992; Kauer-Sant'Anna et al., 2008; Liu et al., 2012; Ridout et al., 2009). The effect of general memory impairment on valence-specific explicit EM performance is unknown and thus may influence the detection of a valence-specific explicit EM bias and/or deficit. Considering these findings, further investigation aimed at identifying the influence of general memory impairment on valence-specific explicit EM performance is warranted. Finally, since no longitudinal studies

were found, questions remain about the role that emotional cognitive patterns may play in the risk of relapse, or in the development of other co-morbid disorders.

Recommendations for future research

Given the neurobiological and neurocognitive differences observed between MDD and BD in previous research (Chiriţă et al., 2015; Fung et al., 2015; Harrison et al., 2018; MacQueen and Memedovich, 2017), it would be useful for future research to investigate explicit EM performance across MDD, BD, and HC groups within a single experimental design. Such direct comparisons will help elucidate differences in explicit EM biases both between MDD and BD *and* between acute mood episodes and euthymia. Given that the most common reasons for excluding studies from the current review were the lack of a structured interview to ascertain psychiatric diagnoses and the use of an interventional methodology, future studies must attain greater methodological consistency when investigating explicit EM biases. To facilitate this, Table 2.2. presents considerations of specific methodological approaches to be used in future research. The use of consistent methodological designs in future research will provide the opportunity for more rigorous analysis (i.e., meta-analysis) across a larger number of studies.

Conclusions

The main conclusion of this systematic review is that current empirical evidence does not readily support the view that acutely depressed individuals with MDD display an explicit EM bias. The current review provides insights into explicit EM in mood disorders with implications for future research. This review highlights the potential importance of several moderating variables that may influence explicit EM performance, including clinical factors (e.g., illness

Table 2.2. Recommendations for future research on explicit EM.

Procedures	Recommendation(s)
Sample Size	Include a sample size calculation.
Inclusion and Exclusion Criteria	Describe the age range (if applicable, stratify results for pediatric and geriatric samples). Define primary and acceptable co-morbid diagnoses; the following are diagnoses that should be the basic exclusion criteria for future EM research: schizophrenia, schizoaffective disorder, delusional disorder, current alcohol and substance use disorder. Current mood status should be explicit; if a euthymic group is included, then criteria for determining euthymia should be described. The use of an HC group matched to the clinical groups on age, sex, gender, IQ, and years of education.
Diagnostic Procedures	The use of a validated diagnostic assessment tool that adheres to the most recent versions of the DSM (American Psychiatric Association, 2013) or ICD (World Health Organization, 2018) is crucial; e.g., the SCID (First et al., 2015). Moreover, the use of mood-specific assessments, such as the BDI (Beck et al., 1996), MADRS (Montgomery and Åsberg, 1979), HDRS (Hamilton, 1960), and/or YMRS (Young et al., 1978) should be included to assess current symptom severity.
Clinically-Relevant Variables	Description of length of illness, number of previous mood episodes, number of hospitalizations, past or current psychosis, suicide attempts, length of euthymia (if applicable), and medication status should all be included.
Encoding Task	Incidental encoding tasks could include a procedure wherein subjects rate the emotional intensity, emotional valence, and/or personal relevance of each stimulus. Incidental encoding tasks prevent subjects from becoming aware of the future memory task, ensuring the outcome measure is baseline (i.e., naturalistic) memory performance and not learning or studying ability. Ratings of subjective valence and personal relevance may also be assessed following the EM task (if not included in the encoding task). EM performance may be stratified according to these phenomena.
Stimulus Type	The use of a normative collection of stimuli is important; e.g., from the IAPS (Lang et al., 1997). Personally-relevant stimuli should be used, when possible, to optimally activate underlying cognitive

	structures, or schemas (Beck, 2008). This may be accomplished by stratifying EM performance according to subjects' self-reported personal relevance ratings provided, for example, during the encoding task (see above recommendation) or after the EM task.
Stimulus Valances	All EM research should include an equal number of stimuli with positive, neutral, and negative valences. Neutral stimuli must be included to rule out the possibility of a general (i.e., unemotional) memory impairment.
Delay Period	A minimum delay period of one day appears to be appropriate to detect true between-group differences in explicit EM free recall tasks. A minimum delay period of one week appears to be appropriate to detect true between-group differences in explicit EM recognition tasks. Future research investigating explicit EM performance using these minimum delay period recommendations will provide more data to either support or refute these hypotheses.
Memory Task	The memory task should be a surprise to all subjects. When employing a recognition task, this should involve presenting all stimuli from the incidental encoding task, plus additional distractor stimuli (an equal number in each valence category). During a recognition memory paradigm, subjects should be presented with a question to indicate whether the stimulus was recognized from encoding (i.e., via a yes/no or know-remember task, analyzed using receiver operating characteristics; see, for example, Yonelinas and Parks, 2007). Free recall should be used to assess recall ability.
Data Analysis and Presentation/Reporting	Data should be analyzed to determine: (1) general memory performance; and (2) explicit EM performance, overall and valance-specific. All descriptive statistics, including means and standard deviations, should be presented alongside any graphical representations of the results, if applicable. Moreover, effect sizes should be included to allow for direct comparisons between studies assessing explicit EM.

BDI, Beck Depression Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; EM, emotional memory; HC, healthy control; HDRS, Hamilton Depression Rating Scale; IAPS; International Affective Picture System; ICD, International Classification of Diseases; MADRS, Montgomery-Åsberg Depression Rating Scale; SCID, Structured Clinical Interview for DSM Disorders; YMRS, Young Mania Rating Scale.

duration, number of depressive episodes, symptom severity, and medication status), stimulus type, encoding strategy, and type of memory retrieval task (e.g., free recall versus recognition). Results of this review also suggest that an extended delay period between encoding and memory retrieval tasks may be particularly important to allow sufficient time for consolidation and detection of an existing explicit EM bias in individuals with mood disorders. Nevertheless, the current findings provide preliminary support against the existence of a mood-congruent explicit EM bias in MDD (however, future research should strive to disentangle the influence of negative stimulus types—e.g., depression-related/sad, anger, disgust, fear, etc.—on mood-congruent explicit EM performance in MDD). Our results also provide preliminary evidence for a potential positive explicit EM bias in acute mania. Finally, given that only one study employing a euthymic sample was included in each clinical population, future research must strive to investigate explicit EM performance in MDD and BD during euthymia to improve our understanding of the pattern of explicit EM across illness stages.

A better understanding of the cognitive patterns of EM in mood disorders is important given that EM may influence mood state, symptom severity, and/or psychosocial functioning. For example, it is hypothesized that there exists a bidirectional relationship between maladaptive cognitive schemas and biased information processing in individuals with depression (and, conceivably, with mania and hypomania; Beck and Bredemeier, 2016). These maladaptive schemas may also be responsible for predisposing individuals to the manifestation of the psychosomatic symptoms of MDD and BD in response to emotionally-arousing stressors (Beck and Bredemeier, 2016). Moreover, the degree of schematic activation may further influence the level of symptom severity. Treatment approaches that help patients control their cognitive response to internal and/or external emotional stressors (i.e., cognitive-behavioural therapy,

emotion regulation therapy) may therefore prove effective at treating the clinical symptoms of an acute mood episode *and* the sub-clinical symptoms of euthymia. In this way, investigation of EM biases in MDD and BD represent an important research focus that may inform potential approaches to non-pharmacological treatments.

Acknowledgements

The authors would like to thank Stephanie Sanger for her peer-review of our search strategy.

Disclosure statement

F.P.K. reports personal fees from Daiichi Sankyo and Janssen-Cilag, grants from Stanley Medical Research Institute (07TGF/1148), grants from INCT (CNPq 465458/2014-9), and from the Canada Foundation for Innovation - CFI, all outside of the submitted work. B.N.F. has received research support from Pfizer. The remaining authors declare no conflicting interests.

Funding

This work was supported in part by the Canadian Institutes of Health Research (Canadian Graduate Scholarships-Master's (CGS-M) Award, B.J.M.B.) and by the Ontario Ministry of Research and Innovation (Early Research Award, B.N.F.; grant number: ER13-09–229).

Author Contributions

B. Bogie and M. Persaud contributed equally to the conception and design of the study, data analysis, manuscript writing, and critical editing.

D. Smith contributed to the design of the study, data acquisition, and manuscript writing.

F. Kapczinski and B. Frey contributed to the conception and design of the study, manuscript writing, and critical editing.

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Supplementary Material

Supplementary File 1. OVID MEDLINE search strategy used in the current systematic review.

1. Depression/
2. exp Depressive Disorder/
3. Cyclothymic Disorder/
4. exp "Bipolar and Related Disorders"/
5. depress*.mp.
6. dysthymi*.mp.
7. dysphori*.mp.
8. cyclothymi*.mp.
9. bipolar.mp.
10. melanchol*.mp.
11. manic.mp.
12. mania.mp.
13. exp Memory/
14. memory.mp.
15. memories.mp.
16. recall.mp.
17. recollect*.mp.
18. retriev*.mp.
19. remember.mp.
20. emot*.mp.
21. bias*.mp.
22. Emotions/
23. Affect/
24. affect.mp.
25. mood congruen*.mp.
26. mood depend*.mp.
27. or/1-12
28. or/13-19
29. or/20-24
30. 25 or 26
31. 27 and 28 and 29
32. 27 and 30
33. 31 or 32

CHAPTER 3

Emotional Reactivity and Explicit Emotional Memory Biases in Major Depressive Disorder During Clinical Remission

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Abstract

Major depressive disorder (MDD) is associated with information processing deficits across several cognitive domains. Two examples include biased reactivity to, and explicit (episodic) memory for, emotional information. Recent research suggests that, compared to healthy controls (HCs), acute depressive states may be associated with reduced reactivity to emotional information in the absence of explicit emotional memory biases; however, our understanding of the cognitive phenotypes of these phenomena during clinical remission (i.e., euthymia) remain unclear. Sixty-one participants completed the current study (30 euthymic MDD, 31 matched HCs). Participants rated the emotional intensity (i.e., emotional reactivity) of 48 negative, 48 neutral and 48 positive images before returning one week later for a surprise recognition memory task. We found main effects of valence across analyses of the emotional reactivity and memory data, such that: (1) both groups displayed higher mean intensity ratings for negative versus positive images, and for positive versus neutral images; (2) both groups displayed reduced memory sensitivity for positive compared to neutral and negative images; and (3) both groups displayed reduced normalized memory sensitivity for positive versus negative images. The euthymic MDD group did not differ from the HC group on emotional reactivity or emotional memory performance. These findings contribute to growing evidence that emotional reactivity and explicit emotional memory may not be affected in individuals with MDD during clinical remission of depressive symptoms.

Keywords: arousal, childhood trauma, cognition, depression, emotion, episodic memory, euthymia, explicit memory, major depressive disorder (MDD), mood disorders, reactivity, remission

Introduction

Major depressive disorder (MDD) is a chronic, disabling condition that affects approximately 4.4% of the global population and is one of the leading causes of disability worldwide (World Health Organization, 2017). A recent population-based study estimated that approximately 11.3% of Canadians experience a lifetime history of MDD (Government of Canada, 2016; Knoll and MacLennan, 2017).

There is wide agreement in the literature that the active stage of MDD is associated with a general impairment in cognitive functioning (Bearden et al., 2006; Pan et al., 2019). For example, acutely depressed MDD participants consistently display dysfunction in the cognitive domains of attention, processing speed, learning, memory, and executive functioning (Pan et al., 2019). Interestingly, recent research has shown that deficits in these same general cognitive domains may persist into the euthymic stage (i.e., clinical remission) of MDD (Bora et al., 2012; Hasselbalch et al., 2011; Preiss et al., 2009). Clearly, MDD is associated with impairments in information processing across both stages of the illness; however, it remains unclear whether this pattern holds for the processing of *emotional* information. In a narrative review of selective literature, Leppänen (2006) found that acutely depressed MDD participants exhibit both attention and memory biases towards negative information. These negative biases are consistent with Beck's (1974, 2008) cognitive model of depression. This model argues that individuals with MDD possess maladaptive cognitive structures, called schemas, that influence information processing across all cognitive domains. In MDD, these schemas tend to be negatively-oriented, resulting in biased reactivity to, and memory for, negative information. Negatively-biased information processing further produces negative beliefs about the self, which ultimately reinforce depressive symptoms.

Research aimed at disentangling the cognitive phenotypes underlying emotional processing across cognitive domains in MDD is an active area of empirical investigation. One such focus involves the investigation of emotional reactivity (ER) and explicit (episodic) emotional memory (EM) in MDD. For example, Bylsma et al. (2008) conducted a comprehensive meta-analysis that supported the emotion context insensitivity hypothesis of ER in MDD during acute depression. This hypothesis posits that acutely depressed individuals with MDD display reduced ER to both negative and positive stimuli; however, questions remain about the persistence of this phenomenon into periods of clinical remission. Furthermore, explicit (episodic) EM is a cognitive sub-domain of EM that involves consciously remembering emotional information (Bradley et al., 1995; Hine and Tsushima, 2018). It is well-established that emotionally-salient information is better remembered than unemotional information by healthy volunteers (Cahill and McGaugh, 1998), and indeed, this phenomenon is supported by a significant body of neurophysiological and neuroimaging research (Cabeza et al., 1997; Cabeza and Nyberg, 2000; Cahill and McGaugh, 1998; Hamann, 2001; Kensinger and Corkin, 2004; LaBar, 2007; LaBar and Cabeza, 2006; LeDoux, 1993; Talmi, 2013; Xu et al., 2017); however, the existence of explicit EM biases across the acute and euthymic stages of MDD remains unclear.

Here, an explicit (episodic) EM bias, hereinafter referred to simply as an explicit EM bias, denotes enhanced explicit memory for experimentally-controlled negative or positive stimuli (Bogie et al., 2019; Matt et al., 1992). Episodic memory is a sub-classification of explicit memory that deals with conscious memory for biographical information (Baddeley, 2001). Interestingly, a recent systematic review concluded that acutely-depressed MDD participants do not, in fact, display a consistent explicit EM bias (Bogie et al., 2019). Research on explicit EM

during the euthymic stage of the illness, however, is much sparser than that during the active stage. Williams et al. (2015) found that pregnant and non-pregnant females with a history of MDD showed impaired EM for negative stimuli compared to matched healthy controls (HCs); however, Arnold et al. (2011) found no such evidence of an EM bias or impairment in euthymic non-pregnant MDD females. Similarly, two recent studies failed to reveal an explicit EM bias in large samples of euthymic MDD participants (Cerny et al., 2019; Ruhe et al., 2019), adding to the growing evidence that no explicit EM bias exists in MDD during periods of euthymia; however, none of these studies investigated explicit EM in a well-characterized sample of euthymic males and non-pregnant females with MDD using a long delay period between encoding and retrieval tasks, which may be important to permit sufficient time for the consolidation of the memory trace and for the detection of an EM bias (Bogie et al., 2019).

To fill this gap, the current study sought to investigate ER and explicit EM biases in euthymic MDD participants compared to matched HCs using a delayed incidental recognition memory paradigm. We originally hypothesized that the euthymic MDD participants would: (1) display reduced ER to negative and positive stimuli compared to HCs, an hypothesis informed by the findings from Bylsma et al.'s (2008) comprehensive meta-analysis; and (2) experience a persistence of maladaptive cognitive schemas, thus displaying an explicit EM bias towards negative stimuli compared to HCs.

Methods

Sample

An *a priori* power analysis using previous memory sensitivity data (Hamilton and Gotlib, 2008) confirmed that a minimum of 30 participants per group would give the current study 80%

power. Thirty euthymic participants with a history of MDD and 31 age/sex/gender/IQ-matched HCs without a lifetime history of mental illness participated in this study. Participants were recruited from the Mood Disorders Program at St. Joseph's Healthcare Hamilton; the Research Participation System through the Department of Psychology, Neuroscience and Behaviour at McMaster University; and from online and community advertisements. This study received ethical approval from the Hamilton Integrated Research Ethics Board (#2247) and all participants provided written informed consent.

A trained clinical researcher administered the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV; First et al., 2015) to assess eligibility. Inclusion criteria for the euthymic MDD group included: (1) a diagnosis of past major depressive disorder; and (2) being euthymic for a minimum of two months prior to study participation. Additional inclusion criteria for all participants included: (1) aged 16-45; (2) the ability to fully communicate in English; (3) the ability to read and consent; (4) a Montgomery-Åsberg Depression Rating Scale (MADRS) score < 8; and (5) a Young Mania Rating Scale (YMRS) score < 8. Participants were excluded if they met any of the following criteria: (1) history of schizophrenia, schizoaffective disorder, delusional disorder, or alcohol or substance dependence; (2) history of alcohol and/or substance abuse in the past six months; (3) history of neurological disease; (4) history of head trauma with loss of consciousness; (5) mental retardation; (6) a current unstable medical condition; (7) imminent risk of suicide; (8) pregnancy; or (9) any change(s) in psychotropic medication(s), including sleep aids, in the past two months.

Measures

Depressive symptoms were assessed using the MADRS (Montgomery & Åsberg, 1979). Manic symptoms were assessed using the YMRS (Young et al., 1978). Circadian rhythm disturbances were evaluated with the 21-item version of the Biological Rhythms Interview Assessment for Neuropsychiatry (BRIAN; Giglio et al., 2009). State and trait anxiety symptoms were assessed with the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1968) *or* the current and general versions of the State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA; Grös et al., 2007).[1] Sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). Abuse and neglect during childhood was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). Baseline intellectual capacity was estimated by the vocabulary and matrix reasoning sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999). Pre-morbid intellectual functioning was assessed using the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001). Height and weight measurements were also taken to calculate body mass index (BMI).

The current study employed validated emotional reactivity (i.e., encoding) and incidental recognition memory tasks (Canli et al., 2000; Hamilton and Gotlib, 2008; Williams et al., 2015). Stimulus material consisted of 72 negative, 72 neutral, and 72 positive images selected from the International Affective Picture System (IAPS; Lang et al., 1997). The IAPS is a database of standardized photographic images with associated normative ratings of valence (i.e., a measure

[1]Anxiety symptoms of the first 35 participants were assessed using the STAI. Anxiety symptoms of the remaining participants were assessed using the current and general versions of the STICSA. This change was made in accordance with evidence showing that the STICSA may be a "purer" measure of anxiety than the STAI (Grös et al., 2007).

of emotional pleasure) and arousal (i.e., a measure of emotional stimulation). Negative images had a mean valence and arousal rating of 3.17 and 5.36, respectively; neutral images had a mean valence and arousal rating of 5.15 and 3.39, respectively; and positive images had a mean valence and arousal rating of 7.22 and 5.03, respectively. A total of 144 IAPS images were used in the reactivity task while all 216 images were used in the incidental recognition memory task (see below). E-Prime v1.2 software was used to code both tasks.

Study procedure

Participants attended two study visits at the St. Joseph's Healthcare Hamilton – West 5th Campus hospital. During the first study visit, written informed consent was obtained. Participants were then administered the clinical questionnaires as per above. The first study visit concluded with participants completing the reactivity task. In this task, participants were seated in a silent examination room and were presented with 144 IAPS images (48 in each valence category) in random order on a laptop. Instructions were provided on-screen and were read aloud to each participant by a trained clinical researcher. The task began with participants viewing a fixation cross in the center of the screen for 1s. Then, a full-screen IAPS image was shown for 3s. Finally, a 7-point Likert scale appeared asking participants to rate the emotional intensity of the image (anchors: 1 = *not emotional at all*, 4 = neutral, 7 = *extremely emotional*; this scale appeared for 7s). This cycle repeated until all 144 IAPS images were presented. Each participant was then invited to return the following week "to complete a similar task" (participants were never informed of the recognition memory task before the second study visit). The second study visit occurred one week after the first study visit. During the second study visit, participants were again assessed on the MADRS and YMRS by a trained clinical researcher to confirm the

maintenance of euthymia. Participants were then instructed about, and asked if they had any prior knowledge of, the incidental recognition memory task (no participants reported prior knowledge of the memory task). During the incidental recognition memory task, participants were shown all 216 IAPS images (72 in each valence category) in random order, which included all 144 images from the first study visit plus 72 new foil images (24 in each valence category). Foil images were matched to the stimuli presented during the first study visit by mean valence and arousal within each of the three valence categories. The incidental recognition memory task began with participants viewing a fixation cross in the center of the screen for 1s. Then, a full-screen IAPS image was shown for 3s. Finally, participants reported whether they had seen each image during the first study visit (there was no time limit enforced on this response). Answer options included: 1 = *I have not seen this picture before*; 2 = *It looks familiar, but I am not sure*; and 3 = *I remember I have seen this picture before*. This cycle repeated until all 216 IAPS images were presented. Following the conclusion of the experiment, participants were orally debriefed and compensated with a $10.00 gift card.

Statistical analyses

Statistical analyses were performed using R software (https://www.r-project.org/). Between-group differences in demographic and clinical characteristics were analyzed using: a chi-squared test for categorical variables; a *t*-test for normally-distributed continuous variables; and a Wilcoxon rank sum test for non-normally-distributed continuous variables.

The procedure for analyzing the reactivity and incidental recognition memory data followed the approach used in Hamilton and Gotlib (2008). Specifically, mean intensity ratings for the negative, neutral, and positive categories were calculated for each group. Given that these

data were not normally distributed, a Scheirer-Ray-Hare test (Dytham, 2011; Mangiafico, 2016), the non-parametric analogue of a two-way analysis of variance, was used to analyze the main effect of group, valence, and their interaction. This test is an extension of the Kruskal-Wallis test and uses ranked data with the assumption that data exist on a continuous scale (Dytham, 2011). 'Group' was introduced as the between-subject factor and 'valence' was introduced as the within-subject factor. *Post-hoc* comparisons were performed using a Dunn's test (Dunn, 1964) with the Benjamini-Hochberg correction for multiple comparisons (Benjamini and Hochberg, 1995; Somerville and Hemmelmann, 2008).

The primary outcome of the EM data was memory sensitivity (*d*') indexes across valence categories. *d'* is a measure of one's ability to accurately discriminate between *signal* (i.e., old stimuli) and *noise* (i.e., new stimuli; Haatveit et al., 2010; Stanislaw and Todorov, 1999). Values of *d'* range from 0 to +∞, with larger *d'* indexes representing a greater ability to discriminate signal from noise (Stanislaw and Todorov, 1999). *d'* indexes were calculated for each participant by using each participant's valence-specific "Hit" and "False Alarm" rates. "Hit" and "False Alarm" rates were calculated as the proportion of correctly and incorrectly identified 2 and 3 responses from the incidental recognition memory task, respectively. *d'* indexes for the negative, neutral, and positive stimuli were then calculated as the difference between the *Z*-transformed "Hit" and "False Alarm" rates using: $d'_v = Z(\text{"Hit"})_v - Z(\text{"False Alarm"})_v$, where 'v' denotes each valence category (Haatveit et al., 2010; Stanislaw and Todorov, 1999). This calculation was performed using the NORMSINV function described in Haatveit et al. (2010). Given that *d'* cannot be calculated when "Hit" = 1 or "False Alarm" = 0, we employed the 1/(2N) rule in these instances to control for extreme proportions (Hautus, 1995; Macmillan and Creelman, 2004). The valence-specific *d'* indexes were then used to calculate normalized d'_{Neg} and d'_{Pos} indexes by

dividing both d'_{neg} and d'_{pos} by d'_{neu}, respectively. A *t*-test was used to compare the d'_{neu} indexes of the MDD and HC groups to assess for a group difference in general memory performance. Both the memory sensitivity and normalized memory sensitivity data were analyzed using the Scheirer-Ray-Hare test (Dytham, 2011; Mangiafico, 2016) and *post-hoc* Dunn's tests (Dunn, 1964) with the Benjamini-Hochberg correction for multiple comparisons (Benjamini and Hochberg, 1995; Somerville and Hemmelmann, 2008). Effect sizes for significant *post-hoc* comparisons were calculated using Vargha and Delaney's *A*, a non-parametric measure of effect size (Vargha and Delaney, 2000). The interpretation of *A* follows: small effect size ($A = 0.56$), medium effect size ($A = 0.64$) and large effect size ($A \geq 0.71$; Vargha and Delaney, 2000).

Finally, given that early life stress has been shown to influence EM performance in MDD during euthymia (see, for example, Gethin et al., 2017), we assessed the degree of correlation between *d'* indexes and total CTQ scores (Bernstein et al., 1994) for the MDD and HC groups. This correlation was assessed using the non-parametric Kendall tau-b (τ_B) rank correlation coefficient (Abdi, 2007; Kendall, 1955; Noether, 1981; Schaeffer and Levitt, 1956).

All tests were two-tailed with statistical significance indicated by $p < 0.05$.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the MDD and HC groups are summarized in Table 3.1. Eleven participants in the MDD group were taking a stable dosage of the following medications: antidepressant ($n = 9$); antipsychotic ($n = 3$); anticonvulsant ($n = 1$); benzodiazepine ($n = 1$); and lithium ($n = 1$). The remaining participants were unmedicated ($n = 19$). Medicated and unmedicated participants did not differ on ER, general memory, *d'* indexes, or normalized *d'*

indexes. Participants in the MDD group met criteria for the following co-morbidities: panic disorder (*n* = 5), generalized anxiety disorder (*n* = 4), social anxiety disorder (*n* = 3), post-traumatic stress disorder (*n* = 3), and obsessive-compulsive disorder (*n* = 1). The average age of onset of MDD was 15.5 ± 2.6 years (median = 15.5, IQR = 3.6) with an average illness duration of 6.6 ± 5.8 years (median = 4.8, IQR = 4.8). Participants in the MDD group reported an average of 3.6 ± 3.6 lifetime major depressive episodes (median = 2.0, IQR = 3.5) and an average of 0.63 ± 2.7 lifetime psychiatric hospitalizations (median = 0, IQR = 0).

Table 3.1. Demographic and clinical characteristics of the participants in the MDD and HC groups.

Variable	MDD (*n* = 30)	HC (*n* = 31)	*P*
Age, years	22.2 ± 5.7	22.3 ± 5.4)	0.62[b]
Sex/gender, F:M	21:10	20:10	0.93[a]
BMI	25.0 ± 5.9	25.4 ± 5.4	0.46[b]
IQ, WASI	107.3 ± 10.9	108.0 ± 9.6	0.79[c]
WTAR	111.7 ± 12.6	114.7 ± 7.6	0.27[c]
MADRS, total score	4.2 ± 2.4	1.7 ± 1.9	**< 0.001**[b]
YMRS, total score	2.1 ± 1.9	0.9 ± 1.3	**0.008**[b]
STAI, state score	36.4 ± 10.8	27.9 ± 4.1	**0.004**[b]
STAI, trait score	47.5 ± 10.8	33.9 ± 4.8	**< 0.001**[c]
STICSA, current score	32.9 ± 10.6	25.5 ± 8.7	**0.02**[b]
STICSA, general score	44.4 ± 15.4	30.1 ± 10.5	**0.01**[b]
BRIAN, total score	48.5 ± 9.7	37.5 ± 10.2	**< 0.001**[b]
PSQI, total score	7.7 ± 3.5	5.1 ± 2.4	**0.001**[c]
CTQ, total score	40.6 ± 10.4	31.6 ± 7.5	**< 0.001**[b]

Note: As described in the Methods section, participants completed the STAI *or* the general and current versions of the STICSA. Thirty-five participants completed the STAI (MDD: *n* = 21; HC: *n* = 14) and the remaining participants completed both versions of the STICSA.
Data are presented as mean ± standard deviation.
[a]Chi-squared test; [b]Wilcoxon rank sum test; [c]*t*-test
BMI: body mass index; BRIAN: Biological Rhythms Interview Assessment for Neuropsychiatry; CTQ: Childhood Trauma Questionnaire; IQ: intelligence quotient; MADRS: Montgomery-Åsberg Depression Rating Scale; PSQI: Pittsburgh Sleep Quality Index; STAI: State-Trait Anxiety Inventory; STICSA: State-Trait Inventory for Cognitive and Somatic Anxiety; WASI: Wechsler Abbreviated Scale of Intelligence; WTAR: Wechsler Test of Adult Reading; YMRS: Young Mania Rating Scale

The MDD and HC groups did not differ in age ($p = 0.62$), with the MDD group having a mean age of 22.2 (median = 19, range: 17-37) and the HC group having a mean age of 22.3 (median = 20, range: 17-38). Analyses also revealed no statistically significant differences between groups on sex/gender (all participants' biological sex matched their self-reported gender identity; $\chi^2(1) = 0.008$, $p = 0.93$) or baseline IQ ($t(59) = 0.27$, $p = 0.79$). The HC group was therefore well-matched to the MDD group on age, sex, gender, and IQ.

Emotional reactivity

Mean intensity ratings from the ER task for the MDD and HC groups are presented in Figure 3.1. A Scheirer-Ray-Hare test failed to find a main effect of group ($H(1) = 0.22$, $p = 0.64$) or an interaction effect ($H(2) = 1.41$, $p = 0.49$); however, a main effect of valence was observed ($H(2) = 113.10$, $p < 0.0001$). *Post-hoc* Dunn's tests revealed that both groups reacted more intensely to: negative than to positive images ($Z = 5.07$, $p < 0.0001$, $A = 0.85$), positive than to neutral images ($Z = 5.56$, $p < 0.0001$, $A = 0.88$), and negative than to neutral images ($Z = 10.63$, $p < 0.0001$, $A = 0.97$). All effect sizes were large.

General memory

Before assessing EM performance, we first assessed whether the MDD and HC groups differed in general memory performance. General memory performance was assessed by comparing the d'_{neu} indexes of the MDD and HC groups. This test revealed that there was no significant difference between the MDD ($d'_{neu} = 2.67$) and HC ($d'_{neu} = 2.88$) groups on general memory performance ($t(59) = 0.76$, $p = 0.45$).

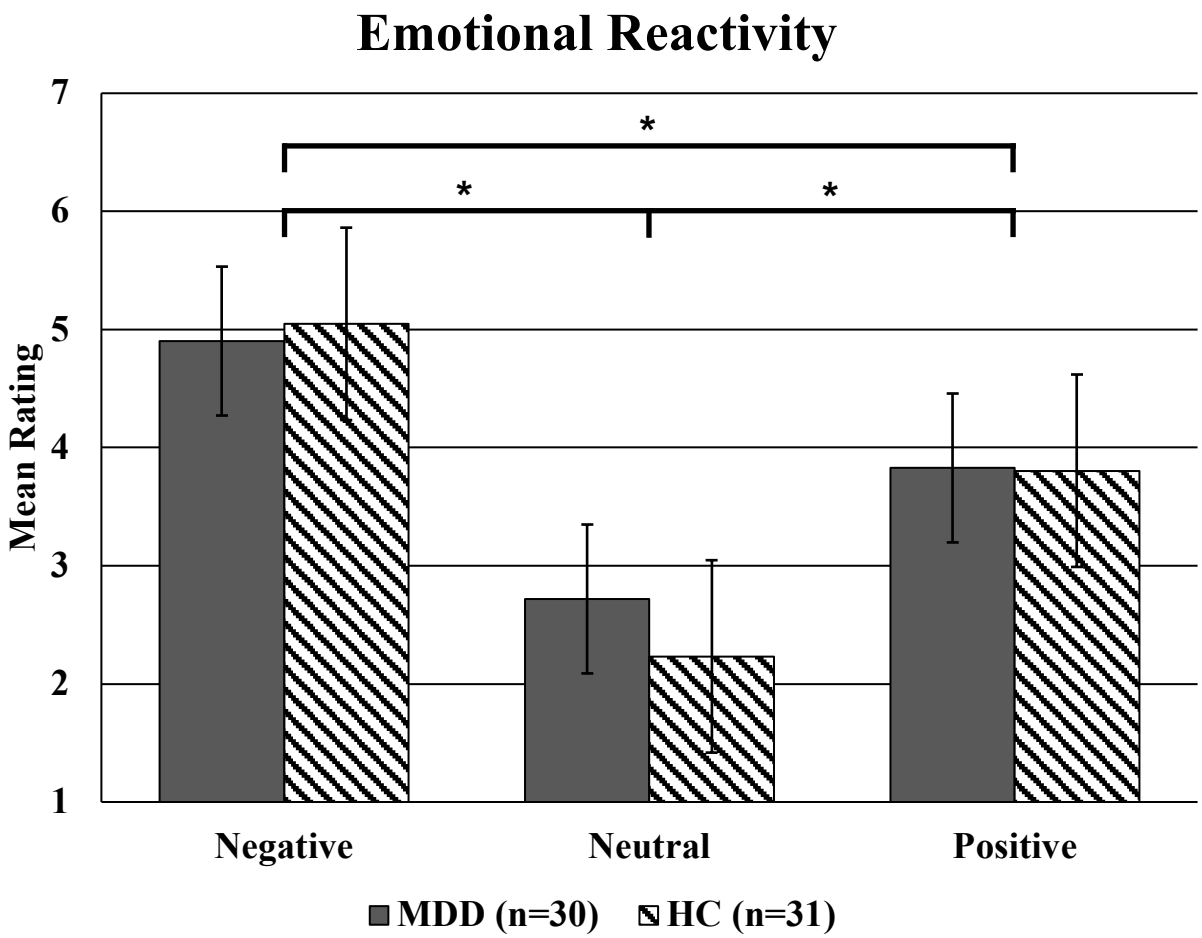

Figure 3.1. Mean emotional intensity ratings (i.e., emotional reactivity) between MDD and HC groups for the negative, neutral and positive images. Data are presented as the mean ± the standard error. *Within-group difference is significant at the $p < 0.001$ level.

Explicit emotional memory

The memory sensitivity indexes (d'_{neg}, d'_{neu}, and d'_{pos}) for the MDD and HC groups are presented in Figure 3.2. A Scheirer-Ray-Hare test again revealed a main effect of valence ($H(2) = 10.21$, $p = 0.006$), but no main effect of group ($H(1) = 0.64$, $p = 0.42$) or an interaction effect ($H(2) = 0.13$, $p = 0.94$). *Post-hoc* Dunn's tests revealed that both groups had greater memory sensitivity for negative than for positive images ($Z = 2.39$, $p = 0.03$, $A = 0.63$; medium effect size) and for neutral than for positive images ($Z = 3.03$, $p = 0.007$, $A = 0.58$; small effect size).

The normalized memory sensitivity indexes for negative (d'_{Neg}) and positive (d'_{Pos}) images (Figure 3.3.) were also analyzed using a Scheirer-Ray-Hare test. This analysis revealed a main effect of valence ($H(1) = 7.63$, $p = 0.006$, $A = 0.65$), but no main effect of group ($H(1) = 0.35$, $p = 0.56$) or an interaction effect ($H(1) = 0.17$, $p = 0.68$). This test revealed that both MDD and HC groups had greater memory sensitivity for negative than positive images after accounting for any variance between groups in general memory performance. The observed effect size for this difference was medium.

Correlation between *d'* indexes and total CTQ scores

The degree of correlation between the d'_{neg}, d'_{neu}, and d'_{pos} indexes and the total CTQ (Bernstein et al., 1994) scores was calculated separately for the MDD and HC groups. Analyses revealed no significant correlation between these variables for the negative (MDD: $\tau_B = -0.17$, $p = 0.19$; HC: $\tau_B = -0.19$, $p = 0.16$), neutral (MDD: $\tau_B = -0.14$, $p = 0.28$; HC: $\tau_B = -0.05$, $p = 0.72$) or positive (MDD: $\tau_B = -0.13$, $p = 0.34$; HC: $\tau_B = 0.05$, $p = 0.69$) valence categories. These results demonstrate that none of the correlation coefficients were significantly different from 0, indicating that the *d'* indexes and the total CTQ scores were not correlated for either group in any valence category.

Discussion

This study investigated ER and explicit EM in a sample of euthymic MDD participants compared against age/sex/gender/IQ-matched HCs. Our main finding was that the euthymic stage of MDD does not appear to be associated with an ER *nor* an explicit EM bias. These results are consistent with very recent findings (e.g., Cerny et al., 2019; Ruhe et al., 2019) that

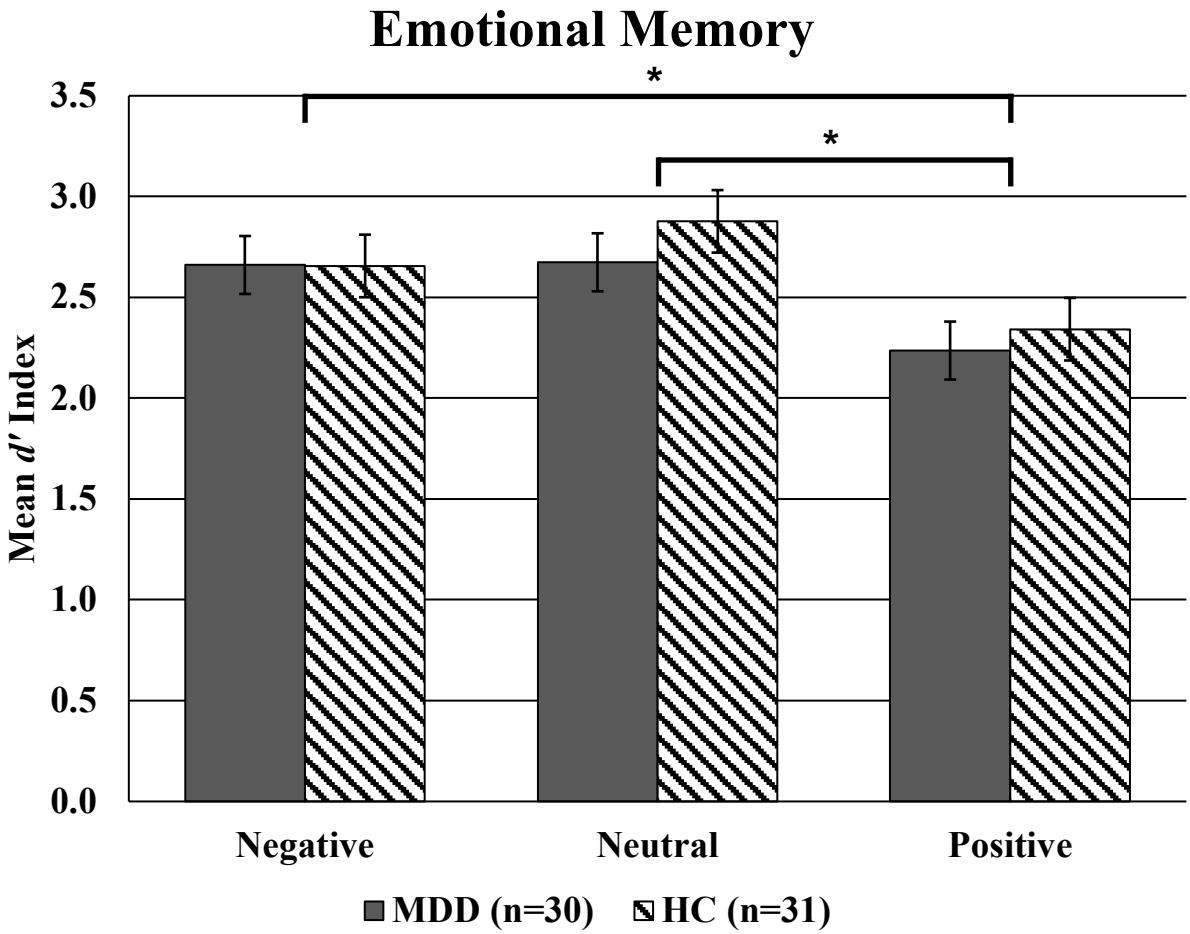

Figure 3.2. Mean memory sensitivity indexes (*d'*) between MDD and HC groups for the negative, neutral, and positive images. The *d'* indexes were calculated according to: $d'_v = Z(\text{"Hit"})_v - Z(\text{"False Alarm"})_v$, where 'v' denotes each valence category (Haatveit et al., 2010; Stanislaw and Todorov, 1999). Data are presented as the mean ± the standard error. *Significant within-group difference ($p < 0.05$).

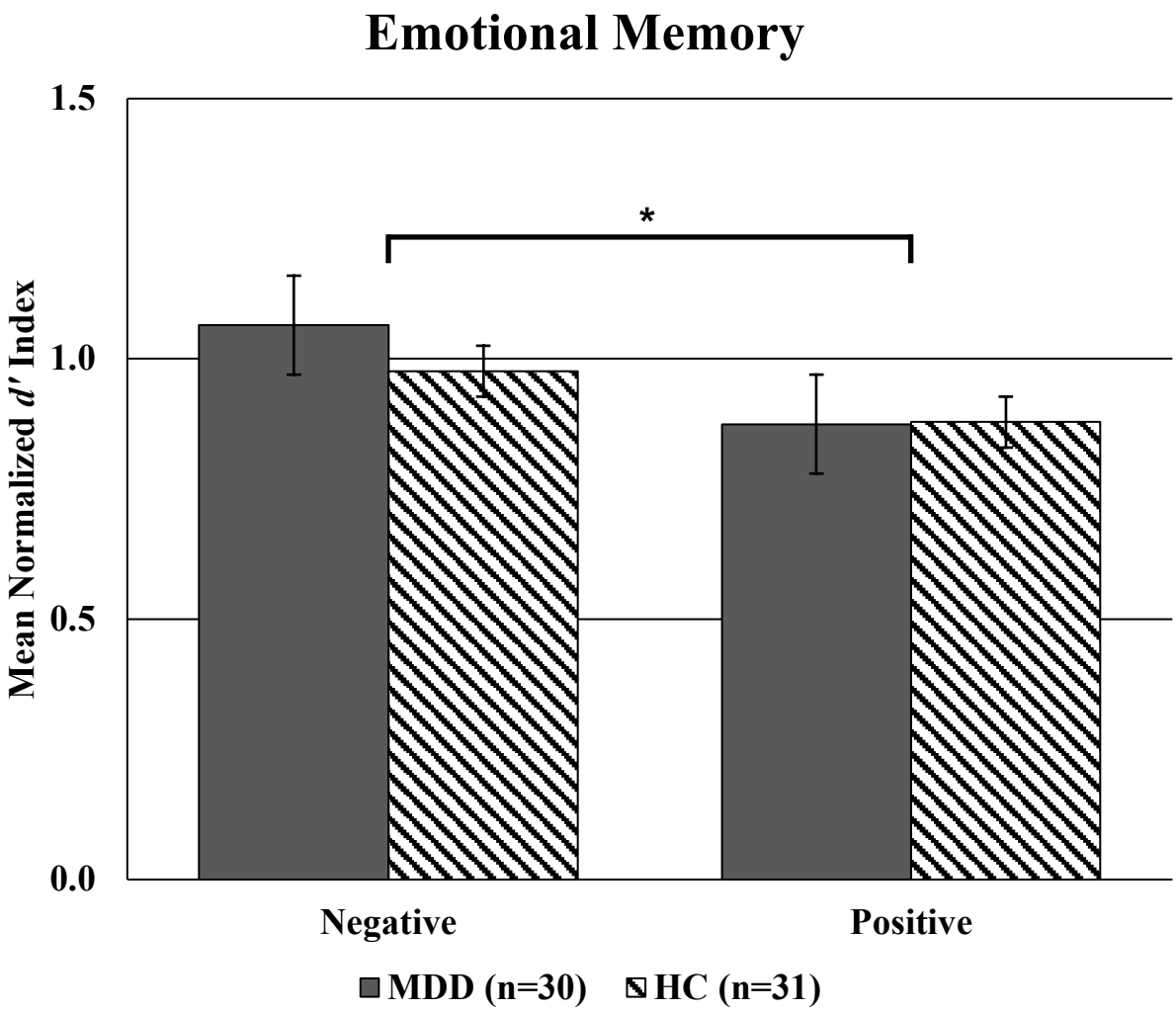

Figure 3.3. Mean normalized memory sensitivity indexes (*d'*) between MDD and HC groups for the negative and positive images. Normalized *d'* indexes were calculated by dividing the negative and positive *d'* indexes by the neutral *d'* index, respectively. Data are presented as the mean ± the standard error. *Within-group difference is significant ($p = 0.006$).

have also demonstrated a lack of an EM bias in euthymic MDD participants. These two studies tested EM over a short delay period (i.e., same-day encoding and memory testing) using emotionally-valent word stimuli; therefore, the current research adds to our understanding of the neuropsychology of MDD during euthymia by investigating EM in a well-characterized euthymic MDD sample using photographic stimuli and employing a one-week delay period between encoding and recognition tasks.

We found that euthymic MDD participants did not differ from HCs on ER to negative, neutral, or positive images. Instead, we found a main effect of valence wherein both the MDD and HC groups reacted more intensely to negative than to positive, and to positive than to neutral, images. This finding does not support our first *a priori* hypothesis; however, this finding does align with recent, converging research investigating ER in MDD during euthymia. For example, using the same methodology as the current study, Williams et al. (2015) showed that pregnant and non-pregnant euthymic women with and without a history of MDD did not differ in ER. The current study replicated these findings in a more representative sample of euthymic males and non-pregnant females.

The current study also confirmed that euthymic MDD participants do not differ from HCs on explicit EM performance (Arnold et al., 2011; Cerny et al., 2019; Ruhe et al., 2019). This finding does not support our second *a priori* hypothesis. We showed that both MDD and HC groups had greater memory sensitivity (*d'*) indexes for negative than positive, and for neutral than positive, images. Furthermore, we showed that both groups had a greater normalized *d'* for negative than positive images. These results indicate that euthymic MDD participants do not display an explicit EM bias towards negative or positive stimuli, even after controlling for variance between groups in general memory performance. Williams et al. (2015) showed that pregnant and non-pregnant women with a history of MDD have impaired EM for negative stimuli; however, this is inconsistent with the current findings and with recent literature. For example, Arnold et al. (2011) showed that euthymic non-pregnant female MDD participants displayed a unique neural processing bias (i.e., compared to HCs, the euthymic MDD participants displayed increased neural activation of the cingulate gyrus; right inferior-frontal and left medial-frontal gyri; right anterior hippocampus; and right amygdala) during the

successful encoding of positive stimuli; however, this neural bias did not translate into an EM bias (i.e., the groups did not differ in EM performance). These researchers argued that this may reflect a neural trait marker of MDD. Even so, there were no neural or cognitive differences between euthymic MDD and HC participants in the successful encoding of negative information; therefore, perhaps Williams et al.'s (2015) finding of a negative explicit EM impairment reflects an altered neural processing mechanism of emotional information specifically associated with pregnancy. Moreover, Cerny et al. (2019) showed that euthymic MDD participants did not differ from HCs on recall *or* recognition memory for negative, neutral, or positive word stimuli (it should be noted, however, that they did find that euthymic MDD participants recognized significantly more negative than neutral words—described as a 'negative affective bias'—compared to HCs). Similarly, Ruhe et al. (2019) also showed that euthymic MDD participants did not differ from HCs on the recall of negative or positive personality characteristics. These findings, along with the results of the current study, contribute to an emerging understanding that the euthymic stage of MDD is not associated with an explicit EM bias.

The current work also demonstrated that the valence-specific *d'* indexes and the total CTQ (Bernstein et al., 1994) scores were not correlated in any valence category for either group. This finding suggest that childhood trauma may not have influenced EM performance in the current work. Recent evidence from Gethin et al. (2017) has shown that, although there were no differences between groups on valence-specific EM accuracy, euthymic MDD participants with a history of early life stress displayed significantly reduced positive bias (i.e., calculated as the accuracy/response speed ratio) compared to MDD participants without a history of early life stress and HCs. These researchers determined the presence of early life stress through a clinical interview. The current study assessed the presence of childhood trauma and neglect through self-

report CTQ (Bernstein et al., 1994) scores. While we found no correlation between EM performance and total CTQ scores, it should be noted that the MDD group reported an average of 'minimal to low' levels of childhood trauma and/or neglect on all of the sub-scales of the CTQ. Therefore, while the MDD group displayed a significantly higher level of childhood trauma and/or neglect than the HCs, the average level was low. Future research into the influence of higher levels of childhood trauma and/or neglect on EM performance may help improve our understanding of whether childhood trauma and/or neglect influences EM performance in MDD during euthymia.

Although the current study failed to find a significant difference between groups in explicit EM performance, it is interesting to note that both the MDD and HC groups recognized significantly fewer positive images compared to negative and neutral images. Similarly, normalization of the *d'* indexes further showed that both groups remembered significantly less positive than negative images. This difference in memory between negative and positive stimuli may be understood when considering that there was a marginal difference between the mean arousal of the negative and positive stimuli used in the current study (MD = 0.33, $SE = 0.14$, $p = 0.052$). It is possible that the positive images may not have evoked a sufficient amount of positive arousal to elicit the same level of EM performance observed in response to the negative stimuli. Nevertheless, our results were consistent across the ER and EM paradigms such that both groups demonstrated greater reactivity and memory towards negative versus positive images.

While a significant body of literature exists suggesting that cognitive impairments in MDD may persist into euthymia (Bora et al., 2012; Hasselbalch et al., 2011; Preiss et al., 2009; Szmulewicz et al., 2017), our results align with growing evidence showing no impairment in

explicit EM *specifically* (Arnold et al., 2011; Cerny et al., 2019; Ruhe et al., 2019), which suggests that explicit EM in MDD may not represent a trait marker of depression. In line with these results, Ruhe et al. (2019) recently found an association between a *task-based* EM score during euthymia and future recurrence of MDD; however, this score was relative to HCs and the comparison of baseline EM performance between the euthymic MDD participants who did and who did not relapse was not significant. These results suggest that EM performance in MDD during a period of euthymia may not be associated with the clinical symptoms of the illness. Indeed, recent work by Porter et al. (2016) showed that psychotherapy (cognitive behavioural therapy or schema therapy) improved clinical outcomes in acutely depressed MDD participants without having any meaningful effect on neuropsychological or emotional processing performance.

In conclusion, ER and explicit EM may not be affected during the euthymic stage of MDD and, combined with recent findings during the acute stage of the illness (Bogie et al., 2019), may not represent a state or trait marker of MDD.

Strengths and limitations

The current study builds upon previous work by investigating ER and explicit EM in a well-characterized sample of euthymic MDD participants. We tested explicit EM performance following a one-week delay period. Recent evidence suggests that the assessment of EM using a recognition memory paradigm should employ a minimum of a one-week delay (Bogie et al., 2019). This extended delay may allow enough time for consolidation of the memory trace and the reliable detection of a memory bias (Bogie et al., 2019). Furthermore, we enforced strict

diagnostic and clinical inclusion/exclusion criteria to control for potential confounding clinical factors, such as changes in mood and/or medications.

Several limitations should be considered when interpreting the results of this study. First, the mean age of the study population was approximately 22, which limits the generalizability of our findings to older individuals with MDD; however, this mean age is consistent with previous studies (Cerny et al., 2019; Rinck and Becker, 2005) and provides the opportunity to draw conclusions about ER and EM in MDD during euthymia in younger adults. Second, although no effect of medication status on ER or EM was observed in the MDD group, over one-third (n = 11) of euthymic MDD participants were taking psychotropic medications. Future research with a larger sample size should investigate whether changes in medication status influence ER and/or explicit EM in MDD. Third, although all participants in the current study were euthymic, participants in the MDD group showed residual symptoms of depression and anxiety, along with higher levels of biological rhythm and sleep disturbances (see Table 3.1.). It is widely recognized that residual symptoms are common among euthymic individuals with a history of MDD (e.g., Israel, 2010); however, a measure of subjective impairment and/or quality of life was not included in the current study. Future research should include such measures to ensure the effects of residual symptoms do not significantly impair patients' psychosocial functioning, and to assess functional remission.

Future directions

Findings from the current study may inform several avenues of future research. First, given that the current study was cross-sectional in nature, future research should strive to investigate ER and explicit EM in MDD longitudinally. For example, the assessment of ER and

EM within a cohort of participants across acute depression, partial remission, and full remission will help elucidate the specific patterns of these phenomena across all stages of MDD. Second, there has been a growing trend in the literature implicating early life stress and/or exposure to trauma as important factors affecting EM performance in MDD (Gethin et al., 2017; Parlar et al., 2018). Future research should further investigate the effect of these phenomena on explicit EM in MDD during euthymia. Finally, future research should investigate the effects of personal relevance and subjective valence interpretations of the experimental stimuli on ER and explicit EM in MDD during euthymia. While the stimuli used in most research assessing explicit EM in MDD are standardized (i.e., IAPS images), participants' personal connection to the content of each stimulus, as well as their own subjective categorization of the stimulus' valence, may be an important factor influencing ER and explicit EM biases in MDD, or the lack thereof.

Conclusions

We found no ER or explicit EM biases in MDD during clinical remission (i.e., euthymia). Our results contribute to growing support for the lack of an explicit (episodic) EM bias in MDD during periods of euthymia (Arnold et al., 2011; Bogie et al., 2019; Cerny et al., 2019; Ruhe et al., 2019). In conjunction with recent work in acutely depressed MDD participants, our results also suggest that ER and explicit EM may not be affected in either the active or euthymic stages of MDD and therefore may not fit the cognitive model of depression (Beck, 1974, 2008).

Acknowledgements

The authors would like to thank Monisha Persaud and Sabrin Salim for their assistance in participant recruitment and data collection. The authors would also like to thank Jee Su Suh for her assistance in data analysis.

Disclosure statement

Bryce J. M. Bogie, Randi E. McCabe, and Margaret C. McKinnon declare no conflicting interests. Flávio P. Kapczinski reports personal fees from Daiichi Sankyo and Janssen-Cilag, grants from Stanley Medical Research Institute (07TGF/1148), grants from INCT (CNPq 465458/2014-9), and from the Canada Foundation for Innovation - CFI. Benicio N. Frey has received research support from Pfizer.

Funding

Bryce J. M. Bogie received a Canadian Graduate Scholarships-Master's Award through the Canadian Institutes of Health Research in support of this work. Margaret C. McKinnon is supported by the Homewood Chair in Mental Health and Trauma at McMaster University. Benicio N. Frey received an Early Research Award from the Ontario Ministry of Research and Innovation (grant number: ER13-09–229) in support of this work.

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CHAPTER 4

Follow-up Study

Introduction and Rationale

While many factors have been identified to influence memory formation (i.e., attention; stimulus arousal and valence; encoding strategy; the effect of timing on consolidation; interference; etc.), little is known about the effect of the personal relevance of the stimuli on explicit EM performance. Previous research suggests that personally-relevant stimuli may facilitate the explicit emotional memory (EM) formation process in major depressive disorder (MDD) during an acute mood episode (Howe & Malone, 2011; Wittekind et al., 2014). For example, Wittekind et al. (2014) recently studied the effect of personal relevance on recognition memory for word pairs (adjective: positive, neutral, or negative; noun: positive, neutral, negative, or depression-related) in a sample of acutely depressed MDD participants compared to healthy controls (HCs). These researchers found that the MDD participants rated the negative and depression-related nouns as significantly more personally-relevant compared to HCs. Furthermore, although there was no difference between MDD and HC groups on their ability to recognize previously-studied word pairs, the MDD group was significantly more likely than HCs to falsely recognize unrelated foil/distractor word pairs that included a personally-relevant noun. Although this study failed to show an effect of personal relevance on veridical memory, evidence from studies employing a self-referent encoding paradigm provide preliminary support for the beneficial effect of personal relevance on veridical memory formation. For example, studies that involve a self-referent encoding paradigm consistently show that participants have more accurate memory for information that is encoded with reference to the self (see Rogers, Kuiper & Kirker,

1977; Symons & Johnson, 1997). How personally-relevant stimuli affect explicit EM in MDD remains an important unanswered question.

Another largely uninvestigated factor that may affect explicit EM performance is the subjectively perceived valence of the stimuli. Research investigating explicit EM tends to use normalized stimuli. One of the most popular normalized stimulus sets is the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 2008). Indeed, several previous studies investigating explicit EM in MDD have used these stimulus materials (e.g., Bogie et al., 2019 [presented in Chapter 3]; Hamilton & Gotlib, 2008; Olsen et al., 2015; Williams et al., 2015). The IAPS is a database of photographic images developed by the National Institute of Mental Health Center for Emotion and Attention at the University of Florida (Lang, Bradley & Cuthbert, 1997). The images in the IAPS database are associated with normative ratings of valence (i.e., a measure of pleasantness), arousal (i.e., a measure of emotional stimulation), and dominance (i.e., a measure of control, ranging from 'in control' to 'dominated'; Bradley & Lang, 2007; Lang, Bradley & Cuthbert, 1997). As of 2007, a total of 16 studies have been conducted to attain the normative valence, arousal, and dominance ratings of the IAPS images (Bradley & Lang, 2007). Each study involved approximately 100 participants (50% female; college students) rating 60 IAPS images on scales of valence, arousal, and dominance (Bradley & Lang, 2007; Lang, Bradley & Cuthbert, 1997). Each scale is designed using the self-assessment manikin (SAM) rating scale (see Figure 2.1 in Bradley & Lang [2007] for a visual depiction of the SAM rating scale). While the IAPS database provides a standardized set of emotional stimuli, the impact of participants' subjectively perceived valence of the stimuli may be an important moderator of explicit EM performance. After all, both valence and arousal are highly dynamic and subjective factors that influence one's subjective experience (Kuppens et al., 2013).

Investigation of the influence of participants' subjectively perceived valence on explicit EM performance is therefore an important gap in the existing literature.

To fill these knowledge gaps, we extended the original work presented in Chapter 3 by devising the current follow-up study. The objective of this follow-up study is to assess the influence of personal relevance and subjective valence categorization on euthymic MDD and HC participants' explicit EM performance. We hypothesize that these factors may reveal differences between the MDD and HC participants on emotional reactivity (ER) and explicit EM performance that were not observed in the original study.

Methods

A Hamilton Integrated Research Ethics Board amendment to assess the effects of personal relevance and subjective valence categorization on ER and explicit EM performance was approved and applied to the original study protocol after 35 participants (MDD: $n = 21$; HC: $n = 14$; i.e., 57.4% of the total final sample of the study presented in Chapter 3) had fully completed the study. Participants who had completed the study were invited by phone and e-mail to complete the new personal relevance and valence categorization tasks. A total of three invitations were extended to participants by phone and/or e-mail.

Sample

In order to attain the minimum power to detect potential between-group differences in ER and explicit EM performance using the amended protocol, this follow-up study targeted a minimum of 30 participants in each of the MDD and HC groups. Recruitment efforts to achieve these group sample sizes are underway.

Measures

Two clinical questionnaires were added to the original study protocol for the purposes of this follow-up study. First, the Depression Anxiety Stress Scale (DASS; Antony et al., 2009) was added as a self-report questionnaire assessing subjectively reported levels of depression, anxiety, and stress. Second, the PTSD Checklist for DSM-5 (PCL-5; Blevins et al., 2015) was added as a self-report questionnaire to assess subjectively reported levels of symptoms related to post-traumatic stress disorder.

A Post-Memory Test Questionnaire was developed to assess participants' personal relevance to, and subjective valence categorization of, each IAPS image (n = 216). This questionnaire was developed and administered through REDCap, a secure online application for the collection and management of survey data. In this task, participants viewed all 216 IAPS images and answered five questions in response to each image. The questions included: (1) 'How personally relevant is this image to you?'; (2) 'How POSITIVE is this image?'; (3) 'How NEUTRAL is this image?'; (4) How NEGATIVE is this image?'; and (5) 'Overall, how would you characterize this image?' Participants responded to questions (1)-(4) using a 7-point Likert scale (anchors: 1 = *not at all*, 4 = somewhat, 7 = *extremely*). Participants responded to question (5) by selecting only one of the following options: positive, neutral, negative. Each IAPS image and all five questions were presented on a single page. There was no time limit enforced on this task.

Study procedure

As mentioned above, participants who fully completed the study before the introduction of the Post-Memory Test Questionnaire were invited to complete the task by phone and e-mail.

Participants who agreed to complete the task were e-mailed a link to the survey and were instructed to complete the task at their earliest convenience. These participants were not required to return to the St. Joseph's Healthcare Hamilton – West 5th Campus hospital to complete the Post-Memory Test Questionnaire. No additional compensation was provided to these participants. Participants who were recruited after the introduction of the Post-Memory Test Questionnaire completed the study procedure described in Chapter 3 (with the addition of the DASS and PCL-5 to the other self-report clinical questionnaires). Following the completion of the incidental recognition memory task during the second study visit, participants completed the Post-Memory Test Questionnaire. This task order was chosen to prevent any confounding effects on the processes of encoding, consolidation, and/or memory retrieval.

Before beginning the Post-Memory Test Questionnaire, participants were required to read and sign the amended study consent form. This requirement was enforced because this task was administered to newly recruited participants *and* participants who had already fully completed the original study in Chapter 3. All participants were given the opportunity to ask questions before providing written informed consent. After providing written informed consent and contact information, participants viewed a total of 217 pages (each page consisted of one IAPS image and the five questions described above). The pages were arranged such that the negative, neutral, and positive images were pseudo-randomly distributed throughout the task. One page that included a neutral image was presented twice to detect potential response bias.

Statistical analyses

All statistical analyses were performed using R software (https://www.r-project.org/). Given that the DASS and PCL-5 data were not normally-distributed, these data were analyzed

using the Wilcoxon Rank Sum test. Mean personal relevance ratings were calculated for the MDD and HC groups across all three valence categories for: (1) the IAPS-designated negative, neutral, and positive images; and (2) the recategorized negative, neutral, and positive images. Given that these data were not normally-distributed, the main effects of group and valence, and their interaction, were assessed using Scheirer-Ray-Hare tests (Dytham, 2011; Mangiafico, 2016), the non-parametric equivalent of a two-way analysis of variance. 'Group' and 'valence' were introduced as the between- and within-subject factors, respectively. *Post-hoc* comparisons were tested using the Dunn's test (Dunn, 1964) with the application of the Benjamini-Hochberg correction for multiple comparisons (Benjamini & Hochberg, 1995; Somerville & Hemmelmann, 2008).

Mean memory sensitivity (*d'*) indexes were calculated on the recategorized IAPS images following the procedure described in Chapter 3. Images were recategorized according to participants' responses to the fifth question of the Post-Memory Test Questionnaire. Given that these data were not normally-distributed, a Scheirer-Ray-Hare test (Dytham, 2011; Mangiafico, 2016) was again performed as described above.

Finally, normalized *d'* indexes were calculated on the recategorized IAPS images for the MDD and HC participants (the procedure for calculating normalized *d'* indexes is described in Chapter 3). Since these data were normally distributed, a two-way analysis of covariance (ANCOVA) was used to assess the main effects of group and valence, and their interaction, on the normalized *d'* indexes. Again, 'group' and 'valence' were introduced as between- and within-subject factors, respectively, and the personal relevance ratings were introduced as a covariate.

Preliminary Results

A total of 33 participants (MDD: $n = 11$; HC: $n = 22$) have completed the follow-up study to-date.

Clinical questionnaires: DASS and PCL-5

Comparison of the DASS and PCL-5 data between the MDD and HC groups revealed that the MDD group reported significantly higher mean levels of subjectively rated depression (MDD: 14.7 ± 13.1, HC: 3.2 ± 6.1; $W = 31$, $p = 0.01$), anxiety (MDD: 10.7 ± 11.0, HC: 3.0 ± 4.9; $W = 33$, $p = 0.02$), stress (MDD: 16.7 ± 12.1, HC: 5.6 ± 8.2; $W = 39.5$, $p < 0.05$), and PTSD-related symptoms (MDD: 27.2 ± 21.2, HC: 8.0 ± 9.4; $W = 35$, $p = 0.03$).

Personal relevance ratings

The mean personal relevance ratings for the negative, neutral, and positive IAPS images and subjectively recategorized IAPS images across the MDD and HC groups are presented in Figure 4.1. Results of the Scheirer-Ray-Hare test on the personal relevance ratings of the IAPS images (Figure 4.1., Left) revealed no main effect of group ($H(1) = 1.66$, $p = 0.20$) or an interaction effect ($H(2) = 0.14$, $p = 0.93$); however, there was a main effect of valence ($H(2) = 10.44$, $p = 0.005$). *Post-hoc* Dunn's tests revealed that both groups rated the positive IAPS images as more personally-relevant than the neutral ($Z = 2.62$, $p = 0.01$) and the negative ($Z = 2.95$, $p < 0.01$) IAPS images. Results of a Scheirer-Ray-Hare test on the personal relevance ratings of the subjectively recategorized IAPS images (Figure 4.1., Right) similarly revealed no main effect of group ($H(1) = 1.11$, $p = 0.29$) or an interaction effect ($H(2) = 0.06$, $p = 0.97$); however, a main effect of valence was identified ($H(2) = 22.57$, $p = 0.00001$). *Post-hoc* Dunn's

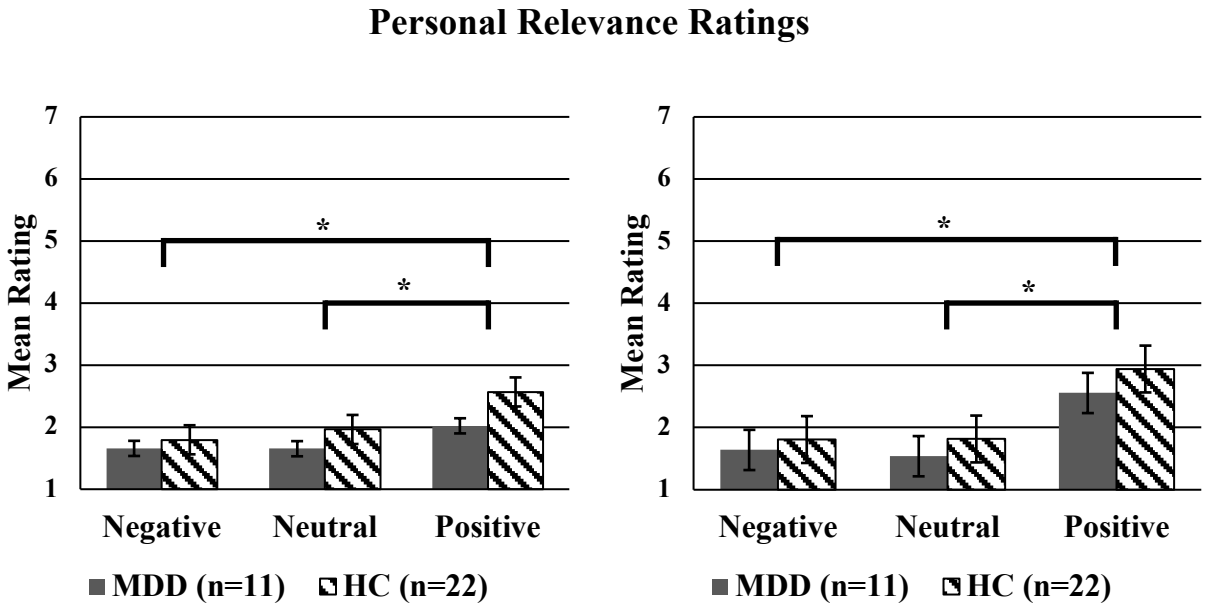

Figure 4.1. Left: Mean personal relevance ratings of the MDD and HC groups across the negative, neutral, and positive image categories. **Right:** Mean personal relevance ratings of the MDD and HC groups across the subjectively recategorized negative, neutral, and positive categories. Data are presented as the mean ± S.E.M. *$p < 0.05$.

tests revealed that both groups rated the positive subjectively recategorized IAPS images as more personally-relevant than the neutral ($Z = 4.29$, $p < 0.0001$) and the negative ($Z = 3.92$, $p < 0.0001$) subjectively recategorized IAPS images. There were no significant differences between both groups' personal relevance ratings between the neutral and the negative IAPS images (i.e., $Z = 0.33$, $p = 0.74$ for the normative IAPS images and $Z = 0.37$, $p = 0.36$ for the subjectively recategorized IAPS images).

Subjective recategorization of the IAPS images

Participants in the MDD group recategorized an average of 59.5 of the 216 (27.5%) IAPS images. Participants in the HC group recategorized an average of 49.6 of the 216 (23.0%) IAPS

images. The average number of IAPS images in each of the three valence categories after subjective recategorization for both groups are presented in Table 4.1.

Table 4.1. The average number of IAPS images in the negative, neutral, and positive valence categories for the MDD and HC groups after recategorization. Data are presented as the mean rounded number of images (± *x*), where *x* represents the average change from baseline (i.e., 72 IAPS images within each valence category).

	MDD (*n* = 11)	**HC (*n* = 22)**
Negative	67 (-5)	67 (-5)
Neutral	107 (+35)	94 (+22)
Positive	41 (-31)	55 (-17)

Emotional memory sensitivity (*d'*) indexes of the recategorized IAPS images

The mean *d'* indexes of the recategorized negative, neutral, and positive IAPS images for both MDD and HC groups are presented in Figure 4.2. Results of the Scheirer-Ray-Hare test on these data revealed no main effect of group ($H(1) = 0.83$, $p = 0.36$), a marginal effect of valence ($H(2) = 5.83$, $p = 0.05$), and no interaction effect ($H(2) = 0.03$, $p = 0.98$).

The mean normalized negative and positive *d'* indexes for both groups are presented in Figure 4.3. The results of a two-way ANCOVA (with personal relevance ratings introduced as the covariate) revealed no main effects of group ($F(1,61) = 0.45$, $p = 0.51$), valence ($F(1,61) = 3.13$, $p = 0.08$), or an interaction effect ($F(1,61) = 0.25$, $p = 0.62$).

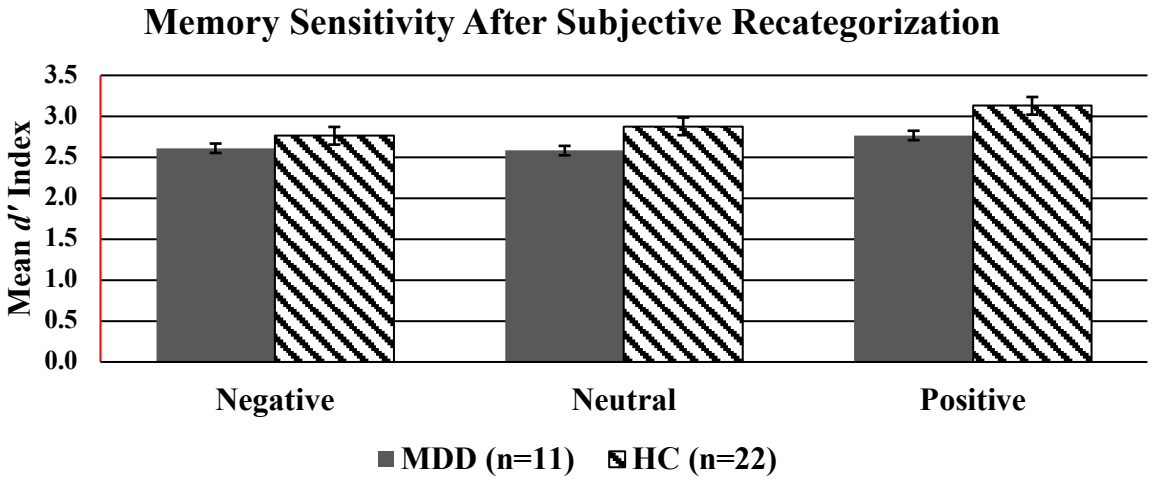

Figure 4.2. Mean *d'* indexes across the negative, neutral, and positive recategorized IAPS images for the MDD and HC groups. Data are presented as mean ± S.E.M.

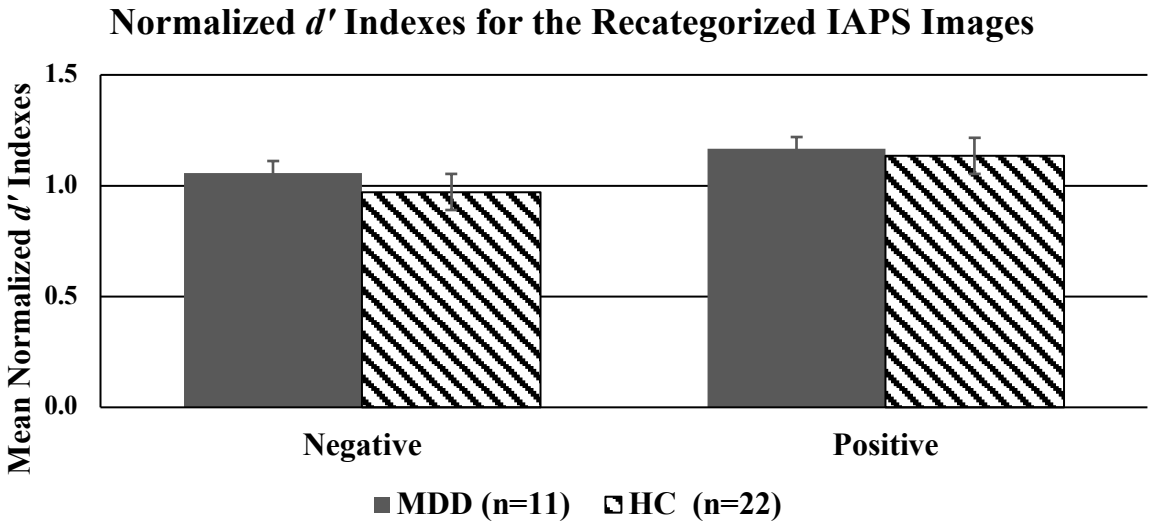

Figure 4.3. Mean normalized *d'* indexes of the negative and positive recategorized IAPS images for the MDD and HC groups. Data are presented as mean ± S.E.M.

Discussion

The results described in this chapter are preliminary in nature and therefore limit the ability to draw firm conclusions. Nevertheless, preliminary analyses revealed that the MDD and HC groups did not differ from one another on the personal relevance ratings for: (1) the original IAPS images (Figure 4.1., Left); or (2) the subjectively recategorized IAPS images (Figure 4.1., Right). A main effect of valence was observed in both cases, with both groups reporting more personal relevance towards the positive images than towards the neutral or negative images. Interestingly, recategorization of the IAPS images seemed to have the greatest influence on the personal relevance ratings for the positive images (i.e., see the positive personal relevance ratings in Figure 4.1., Left versus Figure 4.1., Right).

Both the MDD and HC groups recategorized approximately one-quarter of the original IAPS images (Table 4.1.). This preliminary finding is interesting given that, although the IAPS stimuli are normative/standardized, participants' subjective experience of the stimuli's valence prompted a considerable amount of recategorization. Both groups recategorized a large number of positive images as neutral, with the MDD group recategorizing approximately twice as many positive images as neutral images compared to HCs.

Analyses of the valence-specific *d'* and normalized *d'* indexes (with personal relevance ratings included as a covariate in the latter analysis) after recategorization revealed no main effects of group or valence, or an interaction effect (although a marginal effect of valence was observed, $p = 0.05$). Comparing Figure 4.2. to Figure 3.2. (in Chapter 3), it appears that recategorization of the IAPS images had the greatest impact on participants' explicit EM performance for the positive images (i.e., *d'* indexes for the positive images: $MDD_{original} = 2.24$, $MDD_{recategorized} = 2.77$, $HC_{original} = 2.34$, $HC_{recategorized} = 3.13$). This change likely eliminated the

main effect of valence in the analysis of the *d'* indexes on the recategorized stimuli. Interestingly, recategorization also eliminated the main effect of valence when comparing the normalized *d'* indexes. In fact, recategorization resulted in a shift from the trend observed in our original study (i.e., Figure 3.3.) such that the normalized d'_{Pos} > normalized d'_{Neg} (Figure 4.3.).

Conclusion

Preliminary evidence from this follow-up study supports the conclusion drawn in our original work that MDD participants may not exhibit an explicit EM bias during euthymia. The factors of personal relevance and subjectively rated valence categorization may influence this phenomenon; however, a larger sample size is needed to support this hypothesis. Recruitment is underway to achieve the necessary level of power within the current study.

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CHAPTER 5

General Discussion

The current thesis sought to investigate patterns of explicit emotional memory (EM) in major depressive disorder (MDD) during the acute and euthymic stages of the illness. A systematic review of the scientific literature, presented in Chapter 2, provided a comprehensive understanding of the current knowledge surrounding explicit EM in MDD during both the acute and euthymic stages of the illness. An unintended consequence of this systematic review was the identification of the need for more research investigating explicit EM in MDD during euthymia. Our original research, presented in Chapter 3, helped fill this gap by investigating explicit EM performance in a sample of well-characterized euthymic MDD participants compared to age/sex/gender/IQ-matched HCs. Finally, Chapter 4 further developed our understanding of explicit EM in MDD during euthymia by presenting preliminary results from a follow-up study investigating the phenomena of personal relevance and subjective valence categorization as potential moderating variables influencing explicit EM performance. The main finding of the current thesis was that, contrary to the behavioural patterns predicted to manifest in MDD from the unified model of depression (Beck & Bredemeier, 2016), both the acute and euthymic stages of MDD were not associated with biased explicit EM performance compared to HCs. The aggregate findings from the current thesis are discussed in the remainder of this chapter.

Clinical Characteristics in Major Depressive Disorder During Clinical Remission

Consistent with previous theoretical hypotheses and empirical research, our original work (presented in Chapters 3 and 4) demonstrated a persistence of residual symptoms in a well-

characterized sample of euthymic MDD participants. For example, compared to HCs, the euthymic MDD groups reported in the current thesis demonstrated significantly higher levels of depressive symptoms (both objectively [i.e., MADRS; Montgomery & Åsberg, 1979] and subjectively [i.e., DASS; Antony et al., 1998] rated), manic symptoms, anxiety symptoms, and PTSD-related symptoms. Moreover, compared to HCs, the euthymic MDD group also demonstrated significantly higher levels of biological rhythm disruption, sleep disturbance, and childhood trauma, according to the mean total scores on the BRIAN (Giglio et al., 2009), PSQI (Buysse et al., 1989) and CTQ (Bernstein et al., 1994) questionnaires, respectively. The euthymic MDD participants not only displayed significantly higher total scores on the BRIAN, PSQI, and CTQ compared to HCs, but they also demonstrated significantly higher scores on most of the sub-scales included in these measures (see Appendix B).

The finding that clinical symptoms persist into euthymia supports the unified model of depression by suggesting the persistent activation of maladaptive cognitive schemas into euthymia (Beck & Bredemeier, 2016). As discussed in Chapter 1, these negatively-oriented maladaptive cognitive schemas—which predominate over positively-oriented schemas during a major depressive episode (MDE)—are likely responsible for the manifestation of the cognitive and somatic symptoms of the illness (see Figure 1.1.). During euthymia, the activation of these schemas is reduced, resulting in less severe cognitive and somatic symptoms; however, it appears that, compared to HCs with no history of psychiatric illness, these schemas continue to function maladaptively, manifesting detectable sub-clinical cognitive and somatic symptoms of MDD. Indeed, although the present research enforced a well-defined definition of euthymia as an inclusion criteria (see, for example, Samamé, Martino & Strejilevich [2012] for a discussion of MADRS and YMRS clinical cut-offs of euthymia), the euthymic MDD participants subjectively

reported sub-clinical depressive symptoms, elevated state and trait anxiety (with participants' mean STAI state [Spielberger, Gorsuch & Lushene, 1968] and STICSA general [Grös et al., 2007] scores surpassing previously-defined cut-offs of clinically-significant anxiety; i.e., Julian, 2011; Van Dam et al., 2013), mild stress, and elevated PTSD-related symptoms. The presence of these sub-clinical symptoms further highlights the vulnerability of euthymic MDD patients towards relapsing in response to future stress.

Analyses of the BRIAN (Giglio et al., 2009) and PSQI (Buysse et al., 1989) questionnaire data revealed that, compared to HCs, euthymic MDD participants displayed a significantly greater amounts of biological rhythm disruption and sleep disturbance. The investigation of these specific phenomena in relation to EM is particularly important given that a significant body of literature has identified the role of sleep in the consolidation of emotional memories (see, for example, Nishida et al., 2008; Wagner, Gais & Born, 2001). Interestingly, although both MDD and HC groups met criteria for clinically-defined euthymia at the time of assessment, the euthymic MDD participants reported significantly more disturbances with respect to sleep latency, habitual sleep efficiency, sleep disturbances, and daytime activity compared to HCs (see Appendix B). The subjective report of disturbed sleep and disrupted biological rhythms in MDD during euthymia did not translate into an emotional reactivity (ER) nor an explicit EM bias. Recent evidence suggests that emotional memories may be resistant to decay in response to disturbances in objectively measured sleep (e.g., Cellini, Mercurio & Sarlo, 2019); however, this hypothesis should be investigated in a well-characterized sample of acutely depressed and euthymic MDD participants to determine the effect of objectively measured sleep disturbance(s) on explicit EM performance in MDD specifically.

Finally, analyses of the CTQ (Bernstein et al., 1994) data revealed that the euthymic MDD group subjectively reported significantly higher rates of childhood trauma and neglect *and* childhood emotional and physical abuse and neglect compared to HCs (see Appendix B). Although the mean level of total and sub-scale scores of childhood trauma and neglect were 'low', these levels were higher than those observed in the HC group. This finding is not surprising given that childhood trauma and/or neglect is a recognized risk factor for MDD (Beck & Bredemeier, 2016). Furthermore, as discussed in Chapter 3, the existence of early life stress and/or trauma may have important effects on explicit EM performance. Interestingly, Gethin et al. (2017) recently showed that euthymic MDD participants with a history of early life stress performed significantly worse on a measure of positive associative memory bias (i.e., accuracy/speed ratio) compared to euthymic MDD participants without a history of early life stress and HCs. This preliminary finding supports the unified model of depression's assertion that early childhood trauma (or stress) may give rise to biased information processing phenotypes (Beck & Bredemeier, 2016). We also assessed the correlation between valence-specific memory sensitivity (*d'*) indexes and total CTQ scores (see Chapter 3) and found no correlation between these variables. In an exploratory analysis, we also stratified the total and sub-scale scores of the CTQ according to the presence of trauma exposure (i.e., meeting Criterion A for post-traumatic stress disorder in the SCID-5; First et al., 2015). We found that the trauma-exposed and trauma-non-exposed MDD participants did not differ significantly on the total CTQ score (see Appendix C). Nevertheless, it is interesting to note that one-third of the euthymic MDD sample met the criterion for the presence of trauma exposure. Future investigations of explicit EM in a sample of euthymic MDD participants with higher levels of childhood trauma and/or neglect compared to HCs may improve our understanding of how

exposure to childhood trauma and/or neglect influences explicit EM performance in MDD during euthymia, if at all.

In conclusion, our results support the notion that residual symptoms of MDD persist into the euthymic stage of the illness. This finding may, in part, explain why cognitive impairment is not uncommon in MDD during remission from clinical symptoms. These residual symptoms, along with the underlying cognitive schemas likely responsible for their manifestation, may predispose euthymic individuals with a history of MDD to the onset of future MDEs, especially in response to stressful life events. Treatment and/or preventative approaches that help patients control their cognitive response to environmental stressors (i.e., cognitive-behavioural therapy, emotion regulation therapy) may reduce the risk of relapse in euthymic patients with a history of MDD; however, more direct approaches at rectifying the information processing biases observed in MDD may be more effective (see, for example, Porter et al., 2016).

Emotional Reactivity in Major Depressive Disorder During Clinical Remission

According to the unified model of depression (Beck & Bredemeier, 2016), individuals predisposed to the development of MDD possess maladaptive cognitive schemas that result in negatively-oriented information processing biases (i.e., including ER) compared to HCs. Interestingly, the original research presented in Chapter 3 revealed no differences between the euthymic MDD and HC groups on ER performance. Instead, this research showed that both groups reacted more intensely to negative images than to positive and neutral images (see Figure 3.1.). These results suggest that, compared to HCs, euthymic MDD participants may not demonstrate biased ER towards negative or positive stimuli. These results are consistent with a recent study in pregnant and non-pregnant euthymic women with and without a history of MDD

(Williams et al., 2015); however, research on ER in MDD during euthymia is very sparse and in need of further development.

The pattern of ER in MDD during the acute stage of the illness was investigated by Bylsma, Morris and Rottenberg (2008) in their seminal meta-analysis of 19 studies. They investigated which of the following three prevailing views of ER in MDD were supported by the scientific literature: (1) positive attenuation (i.e., reduced ER to positive information compared to HCs); (2) negative potentiation (i.e., increased ER to negative information compared to HCs); or (3) emotion context insensitivity (i.e., reduced ER to both negative and positive stimuli compared to HCs). They concluded that the available literature supported the third view of ER in which the acute stage of MDD is associated with reduced ER to both negative (Cohen's $d = 0.25$) and positive (Cohen's $d = 0.53$) stimuli, with a greater reduction observed for positive stimuli. This finding clearly does not support a negatively-biased ER phenotype predicted by the unified model of depression. Moreover, the emotion context insensitivity view of ER does not align with the findings obtained from euthymic MDD participants outlined in the current thesis. Questions therefore remain about how the patterns of ER observed during the acute and euthymic stages of MDD fit into the unified model of depression. Perhaps, as suggested by Nesse (2000), the phenomenon of emotion context insensitivity observed during the acute stage of MDD serves an evolutionary purpose to withdraw energy from emotional stimuli. Reduced reactivity to negative and positive stimuli may then serve as a behavioural mechanism wherein one conserves energy by reducing their engagement with the environment. This energy may then be directed towards activities that promote survival, which may include promoting ruminative thinking about the circumstances surrounding the current MDE. The presence of biased ER patterns observed in acute depression may then subside during clinical remission, resulting in no observable

differences between euthymic MDD participants and HCs on ER performance. This would account for the findings reported from euthymic MDD participants (e.g., Williams et al., 2015). In this way, ER may represent a phenomenon that does not readily fit with the unified model of depression, and therefore may represent an exception to this model. This hypothesis must be tested in future research.

Explicit Emotional Memory in Major Depressive Disorder During Clinical Remission

Overall, available evidence is consistent with the existence of a *general* memory impairment in MDD (see, for example, Bora et al., 2013); however, much less is known about the pattern of cognitive performance in MDD for *specific* sub-domains of cognition. The primary purpose of the current thesis was to investigate the presence of explicit EM (i.e., non-autobiographical, conscious EM; Baddeley, 2001) biases in both the acute and euthymic stages of MDD. The operational definition of an explicit EM bias used in this thesis was: heightened memory performance for negative or positive stimuli compared to HCs (Bogie et al., 2019). The main finding of this research was that the acute and the euthymic stages of MDD were not associated with an explicit EM bias.

Acceptance of the existence of negative memory biases in MDD has become almost dogmatic; however, the findings from the current thesis challenge this belief and raise the question: do *all* sub-classifications of memory demonstrate a negative EM bias in MDD? Memory is categorized generally as explicit (i.e., conscious) or implicit (i.e., unconscious; Baddeley, 2001). Explicit memory is further sub-classified as semantic (i.e., factual) or episodic (i.e., biographical; Baddeley, 2001). The current work investigated the existence of EM biases in explicit episodic (non-autobiographical) EM during both the acute and euthymic stages of MDD.

Our finding that the euthymic stage of MDD was not associated with an explicit EM bias is consistent with findings from recent empirical research (i.e., Arnold et al., 2011; Cerny et al., 2019; Ruhe et al., 2019; Williams et al., 2015); however, the current research is the first to demonstrate this finding in a sample of male and non-pregnant female euthymic MDD participants using a one-week delayed incidental recognition memory paradigm. Arnold et al. (2011), Cerny et al. (2019), and Ruhe et al. (2019) all investigated explicit EM in euthymic MDD participants using same-day encoding and memory retrieval tasks, and Williams et al.'s (2015) sample only included female participants. The current work therefore advances our understanding of the patterns of explicit EM in a well-characterized sample of euthymic MDD participants over a relatively longer delay period.

Similar to the ER finding discussed above, the finding that the acute and euthymic stages of MDD may not display a negative explicit EM bias does not fit with the unified model of depression. A tenet of this model is that the cognitive and somatic symptoms of MDD—which may result from, among other things, negatively-oriented information processing biases—are evolutionarily adaptive because they result in the conservation of energy and the promotion of survival (Beck & Bredemeier, 2016); however, explicit EM may be an exception to this hypothesis. Considering that our research failed to identify an explicit EM bias in MDD during either stage of the illness, perhaps the memory biases predicted by the unified model of depression reflect memory for more salient information that is relevant to the self. For example, as discussed in Chapter 1, previous research has identified negative EM biases for autobiographical memories (i.e., memories about the self, based on personal experiences; Köhler et al., 2015). According to the unified model of depression, there is a bidirectional relationship between the cognitive triad (i.e., maladaptive beliefs about the self, the world, and the future) and

negatively-biased information processing (Beck, 1976; see Figure 1.1.); thus, negative autobiographical memories would conceivably manifest strong negative beliefs about the self. This, in turn, may lead to the cognitive and somatic symptoms of MDD. Future research must investigate other sub-classifications of EM in MDD to better elucidate which specific forms of memory constitute negative information processing biases.

Strengths and Limitations

The current thesis represents an aggregate investigation of explicit EM in MDD during both the acute and euthymic stages of the illness. A strength of the systematic review presented in Chapter 2 was the well-defined inclusion and exclusion criteria. These criteria limited the influence of confounding clinical and methodological factors on explicit EM performance; for example, the requirement that participants were unaware of the EM task permitted the development of conclusions about baseline, or naturalistic, explicit EM performance (i.e., without concern for the differential effects of encoding or elaboration strategies that may have been employed by the MDD and HC participants had they known about the subsequent memory task). This was also a strength of the original work presented in Chapters 3 and 4. Together, these strengths allowed conclusions to be drawn about baseline explicit EM performance in well-characterized samples of acutely depressed and euthymic MDD participants.

A clear limitation of the aggregate work presented in this thesis was that explicit EM was investigated in acutely depressed and euthymic MDD participants using a systematic review and an experimental design, respectively. This, in a way, limits the ability to directly compare these populations; for example, it would have been more methodologically sound to investigate

explicit EM by comparing both acutely depressed and euthymic MDD groups to matched HCs using the same experimental design.

Future Directions

The findings from the current work may inform several avenues of future research that might contribute to a better understanding of the patterns of explicit EM observed in MDD during both the acute and euthymic stages of the illness. For example, future experimental investigations of explicit EM in MDD should consider the following research foci:

- The influence of more salient stimuli (i.e., highly-arousing negative and positive stimuli) on explicit EM performance (see, for example, the use of profoundly negative video stimuli by Fitzgerald et al. [2011], which may be used as encoding/memory stimuli for a future explicit EM paradigm).
- The influence of stimulus type (i.e., words, pictures, faces, videos) on explicit EM performance in MDD.
- The influence of a longer delay period (i.e., greater than one week) between encoding and memory retrieval tasks.
- The influence of the type of memory retrieval task (i.e., free recall versus recognition) on explicit EM performance in MDD.
- The influence of demographic and clinical characteristics on explicit EM performance, including explicit EM performance: (1) across age ranges; (2) stratified according to symptom severity, illness duration, number of MDEs, and length of euthymia; and (3) according to medication status.

- The influence of relevant co-morbid diagnoses on explicit EM performance in MDD (i.e., generalized anxiety disorder, post-traumatic stress disorder).
- The influence of trauma exposure and/or early life stress on explicit EM performance.
- The influence of objectively measured sleep quality on explicit EM in MDD (i.e., through the use of actigraphy).
- Investigation of functional remission among clinically-defined euthymic participants and its influence on explicit EM performance in MDD during euthymia.
- The use of clinical questionnaires assessing quality of life (e.g., the Quality of Life Enjoyment and Satisfaction Questionnaire; Endicott et al., 1993) and subjective cognitive impairment (e.g., the Perceived Deficits Questionnaire-Depression; Lam et al., 2018).
- The use of MRI to better characterize and investigate the influence of structural/volumetric changes in the amygdala and/or hippocampus on explicit EM performance in MDD during both illness stages.

Alternatively, it will be important for future research to investigate explicit, implicit, and autobiographical EM performance within the same cohort of MDD participants during both stages of the illness. This research, in conjunction with the considerations outlined above, would inform a better theoretical understanding of the negative information processing biases (i.e., for the cognitive domain of memory specifically) predicted by the unified model of depression (Beck & Bredemeier, 2016).

Conclusions

The main finding of this thesis was that current empirical evidence does not support the existence of a non-autobiographical explicit EM bias in MDD during the acute or the euthymic stages of the illness. Despite showing a persistence of residual symptoms during euthymia, the MDD and HC groups did not differ on ER or explicit EM performance. The phenomena of personal relevance and subjective valence categorization may be important factors that influence ER and explicit EM performance in MDD; however, future research is needed to test this hypothesis.

The findings from this thesis suggests that explicit EM may not represent a state *or* a trait marker of MDD. This finding has implications for the belief that there exists a mood-congruent memory bias for explicit EM in MDD. Our findings raise questions about how explicit EM fits into the current unified model of depression, and if the well-characterized neurological changes observed in MDD affect all memory processes equally.

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APPENDIX A

The ethnic composition of the euthymic MDD and HC groups from the original research presented in Chapter 3 is summarized below. Data are presented as: frequency (%).

Ethnicity	MDD (*n* =30)	HC (*n* = 31)
Not Specified	1 (3.3)	
Afghan	1 (3.3)	
African American	3 (10.0)	1 (3.2)
Asian	8 (26.7)	10 (32.3)
Caucasian	13 (43.3)	17 (54.8)
Middle Eastern	1 (3.3)	2 (6.5)
Mixed		1 (3.2)
Native American	1 (3.3)	
Persian	2 (6.7)	

APPENDIX B

The sub-scale scores of the BRIAN (Giglio et al., 2009), PSQI (Buysse et al., 1989), and CTQ (Bernstein et al., 1994) used in the original research presented in Chapter 3 are summarized below. Data are presented as: mean (standard deviation).

Questionnaire, sub-scale	MDD (*n* = 30)	HC (*n* = 31)	*P*
BRIAN, sleep	12.8 (3.2)	9.7 (3.1)	**<0.001**
BRIAN, activity	10.6 (3.4)	7.3 (2.8)	**<0.001**
BRIAN, social	8.3 (2.7)	6.0 (2.6)	**<0.001**
BRIAN, eating	10.0 (3.5)	8.0 (2.8)	**0.03**
BRIAN, chronotype	6.4 (1.5)	6.6 (1.4)	0.99
PSQI, subjective sleep quality	1.2 (0.7)	1.0 (0.5)	0.15
PSQI, sleep latency	1.7 (1.1)	0.9 (0.8)	**0.006**
PSQI, sleep duration	0.9 (0.9)	0.8 (0.7)	0.92
PSQI, habitual sleep efficiency	0.9 (1.0)	0.5 (0.8)	**0.04**
PSQI, sleep disturbances	1.4 (0.6)	0.8 (0.4)	**0.003**
PSQI, use of sleep medication	0.1 (0.4)	0.1 (0.5)	0.67
PSQI, daytime dysfunction	1.5 (0.9)	0.8 (0.6)	**<0.001**
CTQ, emotional abuse	10.4 (4.2)	7.6 (3.6)	**0.002**
CTQ, physical abuse	6.5 (2.4)	5.4 (0.8)	**0.01**
CTQ, sexual abuse	5.7 (2.2)	5.0 (0.0)	0.09
CTQ, emotional neglect	11.0 (3.5)	7.8 (3.5)	**<0.001**
CTQ, physical neglect	7.0 (2.6)	5.8 (1.6)	**0.02**

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APPENDIX C

The mean CTQ (Bernstein et al., 1994) total score and sub-scale scores of the MDD group used in the original research presented in Chapter 3 are summarized below with respect to trauma exposure. Here, 'trauma exposed' denotes meeting Criterion A for post-traumatic stress disorder in the SCID-5 (First et al., 2015). The two groups did not differ in total CTQ score ($p = 0.27$).

	Trauma Exposed ($n = 10$)	**Not Trauma Exposed ($n = 20$)**
Emotional abuse	10.8	10.2
Physical abuse	6.4	6.6
Sexual abuse	7.0	5.1
Emotional neglect	11.7	10.6
Physical neglect	7.9	6.5
Total score	43.8	39.0

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