COGNITIVE REMEDIATION IN PATIENTS WITH MOOD DISORDERS

COGNITIVE REMEDIATION IN PATIENTS WITH MOOD DISORDERS: BEHAVIOURAL AND NEURAL CORRELATES

By

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ABSTRACT

This thesis presents research documenting the effectiveness of computer-assisted cognitive remediation for patients with mood disorders. The first chapter provides an overview of cognitive impairment in patients with bipolar disorder (BD) and major depressive disorder (MDD), and a concise review of cognitive remediation in patients with schizophrenia, where the efficacy of these interventions has been reasonably well studied. The results of an analysis comparing neuropsychological test performance in patients with BD, MDD, and healthy controls is presented in Chapter 2, where we show a similar degree of deficit in both patient groups on processing speed, working memory, and mental flexibility tasks, and a greater degree of deficit in patients with BD on delayed recall and verbal fluency tasks. In Chapter 3 we present the results of our primary analysis examining the effectiveness of CACR for patients with BD and MDD; we show significant improvement on neuropsychological tests of working memory and delayed memory following remediation, and positive associations between improvement in neuropsychological test performance, and improvement in subjectively-rated cognitive and psychosocial functioning. Finally, in Chapter 4 we present functional neuroimaging evidence that shows increased activation following cognitive remediation in frontal control regions supporting working memory and in the right hippocampus supporting recollection memory. Although

behavioural performance on the corresponding tasks was stable, the observation of increased activation in frontal and medial temporal brain regions following remediation is in line with our finding of improvement on neuropsychological tests of working memory and delayed recall post-training. Taken together, the results presented in this thesis provide convergent behavioural and neural evidence to demonstrate the efficacy of computer-assisted cognitive remediation for patients with mood disorders. These novel findings contribute to a growing body of literature that shows cognitive remediation to be an effective cognitive management strategy across a range of psychiatric and neurological disorders.

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LIST OF ABBREVIATIONS

ANOVA/ANCOVA	……Analysis of Variance/Analysis of Covariance
A/P	……Anterior/Posterior
BA	…….....Brodmann Area
BD	……..Bipolar Disorder
BOLD	……Blood Oxygenation Level Dependent
CACR	……Computer-Assisted Cognitive Remediation
COWAT	……..……Controlled Oral Word Association Test
DSM-IV	…….Diagnostic and Statistical Manual of Mental Disorders
DSS	……..Digit Symbol Subtest
DS/DS-F/DS-B	……...Digit Span/Digit Span Forward/Digit Span Backward
ECT	……Electroconvulsive Therapy
fMRI	……...Functional Magnetic Resonance Imaging
FOV	……..Field of View
GLM	……General Linear Model
HC	……...Healthy Control
HRSD	……Hamilton Rating Scale for Depression
HVLT	……...Hopkin's Verbal Learning Test
IRP	……...Inversion Recovery Prepped
LSP	……Life Skills Profile
MDD	……Major Depressive Disorder
MR	……...Magnetic Resonance
NART-estVIQ	……..National Adult Reading Test Estimated Verbal Intelligence Quotient
Q-LES-Q	……...Quality of Life Enjoyment and Satisfaction Questionnaire
SCID-I/P	……...Structured Clinical Interview for the DSM-IV, Patient Version
SF-36	……..Short Form Health Survey
TE	……...Echo Time
TMS	……Transcranial Magnetic Stimulation
TMT/TMT-A/TMT-B	……....Trail Making Test/Trail Making Test-A/Trail Making Test-B
TR	……...Repetition Time
WAIS-R	……Wechsler Adult Intelligence Scale-Revised
YMRS/YMS	……Young Mania Rating Scale
3D SPGR	……..Three-Dimensional Spoiled Gradient Recalled Acquisition in Steady State

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis contains a total of five chapters: Chapters 2 through 4 are empirical journal articles; Chapter 1 provides a background context for the work; and Chapter 5 discusses the clinical implications of the main findings. Data collection for the empirical papers was ongoing between November 2007 and November 2010. Patients with BD and MDD were recruited through the Mood Disorders clinic at St. Joseph's Healthcare, Hamilton to participate in a 10-week trial of computer-assisted cognitive remediation. Patients were tested on a battery of neuropsychological tasks and quality of life measures at a baseline time point (PRE), immediately following the intervention (POST; approximately 3 months after baseline testing), and again 3 months later (FLW-UP). As well, patients participated in two functional imaging scans at PRE and POST to examine the neural correlates of working memory and recollection memory pre- and post-intervention. A group of healthy control subjects were tested using the same neuropsychological and quality of life battery at the same three time points to control for test-retest effects in the patient sample. These subjects did not participate in the cognitive intervention, however. Healthy controls were scanned once during either a working memory task or a recollection memory task, for the purpose of contrasting activation in the patient sample at baseline with that of a normative sample.

This study was designed by Dr. Glenda MacQueen. Behavioural data collection was supervised by Drs. Margaret McKinnon and Kathy Macdonald, and collection of the functional imaging data was supervised by Dr. Geoffrey Hall. I oversaw all aspects of the research including study coordination, data collection, and data management. Ms. Helen Begin, RN, CCRA, CCRC, CPMHN(c) was the clinical research coordinator for the study and was responsible for recruitment and screening of participants. Four research assistants and several members of the McKinnon and Hall labs assisted with data collection, including: Amy Bustamam, Katherine Holshausen, Jason Bosett, Sarah Begin, Matthew King, Andree Cusi, Shelley Ferris, Laura Garrick, Andrea Milne, Caitin Gregory, and Philp Fougere. I was responsible for preprocessing of the functional imaging data, analysis of the behavioural and functional data, and manuscript preparation. This research was supported in part by an operating grant from Astra Zeneca, and by the Ontario Mental Health Foundation (OMHF) in the form of a research studentship awarded to myself. Portions of this work were presented at the 2010 Society for Biological Psychiatry Meeting in New Orleans, LA and the 2010 annual meeting of the Canadian Psychiatric Association in Toronto, ON.

The paper presented in Chapter 2 (*Comparison of the pattern of cognitive deficit in patients with bipolar disorder or major depressive disorder*) was submitted for review to *Psychiatry Research* in September, 2011. This paper uses neuropsychological test data collected at the baseline (PRE) time point. This paper also includes baseline neuropsychological test data that was collected as

part of another ongoing study of cognitive functioning in patients with BD and MDD (Principal Investigator: Dr. Glenda MacQueen).

The paper presented in Chapter 3 (*A controlled trial of cognitive remediation on cognition and quality of life in patients with mood disorders*) was submitted for review to the *British Journal of Psychiatry* in November, 2011. The efficacy analysis outlined in this paper uses the neuropsychological and quality of life data collected at PRE, POST, and FLW-UP time points. We also conducted an analysis to examine the effects of depressive symptom severity, medication load, motivation/engagement, and baseline level of impairment on the efficacy of cognitive remediation. This analysis included data that were collected during a preliminary study of cognitive remediation in patients with MDD using the same training program (Elgamal et al., 2007).

The paper presented in Chapter 4 (*Neural correlates of cognitive remediation in patients with mood disorders*) was submitted for review to the *Archives of General Psychiatry* in September, 2011. This paper uses patients' functional imaging data collected before and immediately after the intervention (PRE and POST). The normative data used for comparison purposes were collected from one group of healthy control subjects scanned during the working memory task, and another group of healthy control subjects scanned during the recollection memory task.

CHAPTER 1

GENERAL INTRODUCTION

This thesis outlines behavioural and functional imaging research concerning the effectiveness of computer-assisted cognitive remediation for patients with mood disorders. The use of these programs for managing cognitive impairment has been reasonably well studied in patients with schizophrenia (McGurk et al., 2007b; Grynspan et al., 2011); however their efficacy for patients with mood disorders has only been examined preliminarily (e.g., Elgamal et al., 2007; Naismith et al., 2010; Deckersbach et al., 2010). This thesis extends extant findings of short-term cognitive improvement following training; we measured neuropsychological and psychosocial functioning in patients with bipolar disorder (BD) and major depressive disorder (MDD) before and immediately after a 10-week computer-assisted cognitive remediation (CACR) program, and again 3 months after cessation of the program. As a means of exploring the neurobiological changes that mediate improvement following remediation—an area of research that has received little attention to date—patients also underwent functional magnetic resonance imaging (fMRI) scans during a working memory task and a recollection memory task, before and immediately after the intervention.

The following overview is divided into three sections, to provide a concise summary of the extant literature relevant to the three experimental studies

presented within this thesis. In the first section, we review evidence of cognitive dysfunction in patients with BD and MDD. Although trait-related cognitive deficits are reliably documented in both of these patient groups, further research is needed to determine how these groups compare to each other, in terms of pattern and degree of deficit. We address this issue in Chapter 2 with an empirical analysis that contrasts cognitive functioning in patients with BD and MDD directly. Here, we show that patients with BD and MDD differ primarily in degree—not pattern—of deficit. A better understanding of how these two diagnostic groups perform on tests of neuropsychological functioning relative to each other may inform endophenotype research. Moreover, the degree of overlap in pattern of deficit between patients with BD and MDD makes it likely that both groups would benefit from structured remediation programs that emphasize similar areas of cognitive deficit.

In the second section we review the use of cognitive remediation as a treatment strategy for cognitive deficit. We focus our attention on schizophrenia, because this is where the majority of research on cognitive remediation in psychiatric populations has been carried out. In fact, there are over twenty randomized controlled trials of cognitive remediation in patients with psychotic-spectrum disorders that demonstrate immediate and sustained improvement across several domains of functioning, including processing speed, working memory, episodic memory, and executive functioning (McGurk et al., 2007b; Grynspan et

al., 2011). In Chapter 3 we present the results of a 10-week trial of cognitive remediation for patients with mood disorders, where we show similar benefits to this patient group in domains of memory, and in perceived level of functioning. We also show that severity of cognitive impairment and medication load are not barriers to successful response; thus, cognitive remediation has the potential to be widely beneficial for patients who experience cognitive dysfunction associated with a primary mood disorder.

We review the neural correlates of working memory and recollection memory in the third section; in particular, we focus on imaging studies that compare patients to healthy controls on tasks tapping these domains. The majority of these studies show key structural and functional abnormalities in the neural substrates that mediate task performance, namely, in frontal control regions and in medial temporal lobe structures. In Chapter 4 we explore the potential for neuroplastic change within these memory networks following a course of cognitive remediation. First, we confirm the expected pattern of task-related functional abnormality across frontal and temporal memory networks in a large sample of patients diagnosed with a primary mood disorder, relative to a sample of healthy control subjects. Next, in a subsample of these patients who were scanned before *and* immediately following the 10-week intervention, we show significant increases in activation post-remediation within frontal and temporal memory networks; in lateral and medial prefrontal regions that support attention

and working memory, and in medial temporal regions that subserve recollection memory. These results provide some of the first evidence for functional change following cognitive remediation in patients with mood disorders.

1.1 Cognitive deficits in mood disorders

In addition to affective and neurovegetative symptoms, cognitive deficits are increasingly recognized as a core feature of mood disorders. These deficits are most pronounced during acute mood episodes (Kurtz & Gerraty, 2009; McDermott & Ebmeier, 2009), but are reliably present in the euthymic state as well, regardless of residual mood symptoms or medication use. For example, recent meta-analyses of cognitive functioning in euthymic patients with BD show large effect sizes ($d > 0.8$) across domains of sustained attention, set shifting, and verbal learning; medium effect sizes ($0.5 < d > 0.8$) across domains of processing speed, verbal memory, working memory, response inhibition, verbal fluency, and concept formation; and small effect sizes ($0.2 < d > 0.5$) across domains of visuoperception and visual memory (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009). The pattern of cognitive deficit in euthymic MDD has been less rigorously studied; however, there is evidence of impairment in domains of attention, psychomotor speed, memory, and executive function (e.g., Nakano et al., 2008; Paelecke-Habermann et al., 2005, Biringer et al., 2007). Critically, in both patient groups, cognitive impairments can be detected early in the course of illness, and to a lesser extent in first-degree relatives (Bora et al.

2009; Brotman et al. 2009; Savitz et al. 2007; Sarosi et al. 2008). These findings raise the possibility that some of these cognitive deficits reflect endophenotypic traits, in particular for patients with BD where the majority of criteria for identification of an endophenotype have been satisfied (see MacQueen et al., 2005 for a detailed overview).

Endophenotypic traits—whether neuroanatomical, neurophysiological, or neuropsychological—are "reduced" indices of functioning that can provide a more direct link to the genetic underpinnings of a particular disorder or group of disorders (Gottesman & Gould, 2003). These simpler and more objective phenotypic measures are particularly relevant to psychiatry where clinical presentations can be multifaceted and heterogeneous. A complex behavioural gestalt may be difficult to decompose, but the presence or absence of a particular endophenotypic trait could be a useful means of diagnostic clarification, or may help identify some of the neuropathological or maladaptive neurocognitive processes that contribute to the development and maintenance of a particular disorder. Targeting these processes through pharmacological means or therapy may aide in optimizing treatment response and functional outcome.

It remains to be determined the extent to which cognitive endophenotypes can be used to enhance diagnostic reliability or treatment of BD and MDD, however. Relatively few research studies have compared directly the cognitive profile of individuals with BD and MDD (e.g., Bora et al. 2010; Hill et al. 2009),

and even fewer have documented this comparison in euthymic or stable patients. Moreover, those data that do exist are conflicting: one study suggests greater relative impairment in patients with MDD (Paradiso et al., 1997), others suggest that patients with BD may be more impaired (Smith et al., 2006), particularly following remission of mania (Gruber et al. 2007). Another yet found a similar degree of deficit in remitted patients with BD and MDD (Stoddart et al. 2007).

To clarify these findings, in Chapter 2 we present a comparison of neuropsychological functioning between patients with BD, patients with MDD, and a matched healthy control group. The extant literature in euthymic BD reliably shows performance decrements on measures of set shifting, processing speed, delayed verbal memory, and working memory (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009); accordingly, we expected that patients with BD would show impairment, relative to healthy controls, on tests tapping these domains. In patients with MDD neuropsychological impairments are relatively well characterized during acute mood episodes; however, we have yet to reach a consensus on the neuropsychological profile of remission. Some studies show widespread and nonspecific cognitive deficits across domains of information processing, attention, memory, and executive functioning (Reppermund et al., 2009), whereas others report specific deficits in some, but not all, domains assessed (Paelecke-Haberman et al. 2005; Clark et al. 2005a; Clark et al., 2005b; Nakano et al. 2008; Reischies & Neu, 2000). Based on

the weight of evidence, we predicted significant impairment in patients with MDD, relative to healthy control subjects, on working memory and executive tasks (i.e., set-shifting and verbal fluency). We also predicted that patients with MDD would show a similar degree of impairment on these tasks relative to patients with BD. The findings from this analysis will have implications for endophenotype research; i.e., research that aims to identify the genetic underpinnings of a particular disorder or group of disorders by linking phenotypic—or trait-related—characteristics to a particular genotype. This work also has the potential to guide the development of cognitive management strategies that optimally target domains of functioning relevant to individuals with mood disorders.

1.2 Cognitive remediation

Regardless of diagnosis, cognitive impairment is a significant predictor of poor functional outcome. In patients with BD, neurocognitive deficits increase the risk of impairment in work, family, and social domains (Sanchez-Moreno et al., 2009; Wingo et al., 2009; Altshuler et al., 2008; Martinez-Aran et al., 2007; Martino et al., 2009; Bonnin et al., 2010), and are associated with poorer self-rated quality of life (Brissos et al., 2008). Although this issue has been studied to a lesser extent in patients with MDD, the findings are similar. Baseline neurocognitive scores were predictive of psychosocial functioning at a 6-month follow-up visit in patients with MDD. Moreover, neurocognitive performance at

the 6-month visit was strongly associated with level of functioning, even after residual depressive symptoms were covaried (Jaegar et al., 2006). These findings underscore the importance of considering cognitive impairment as part of a comprehensive treatment strategy.

The primary non-pharmacological intervention that targets cognitive impairment is cognitive remediation. Cognitive remediation was originally developed for patients with brain injury (Luria, 1963; Luria et al., 1975), and rehabilitative efforts in this population took a compensatory approach; patients learned alternative strategies and skills to replace functions that were damaged or deficient following injury. Strategy-based remediation has also proven effective for stroke rehabilitation (Cicerone et al., 2005; Rohling et al., 2009), and for managing normal age-related cognitive decline (Levine et al., 2007; Winocur et al., 2007; Vance et al., 2008).

More recently, however, advances in knowledge about plasticity within the central nervous system have led to the development of restitution-based methods of remediation. These approaches target neural networks that are dysfunctional or damaged beyond the point of spontaneous recovery, but not beyond the point of complete loss of function. Precisely targeted "bottom-up" and "top-down" stimulation of a dysfunctional neural network exploits principles of experience-dependent plasticity and Hebbian learning to guide repair and recovery of function (see Robertson & Murre, 1999 for discussion). As such,

restitution-based approaches to remediation involve extensive, repetitive practice. Initially, patients perform tasks in a single cognitive domain (e.g., attention), followed by multi-domain tasks (e.g., attention and memory), and, once successful, graduate to complex tasks that rely upon problem solving skills. This hierarchical task sequence allows for the stabilization and consolidation of lower-level skills before higher-level functions are recruited and strengthened.

Cognitive remediation programs are becoming more widespread, particularly for patients with schizophrenia, where the efficacy of these interventions has been studied extensively. There are over twenty randomized controlled trials that demonstrate immediate and sustained improvement across several domains of cognitive functioning—including processing speed, working memory, episodic memory, and executive functioning—following a cognitive remediation intervention (e.g., Medalia et al., 1998; Medalia et al., 2001; Penades et al., 2006; Kurtz et al., 2007). The positive effect of cognitive remediation on functional outcome and quality of life is also well-established (Bell et al., 2005; McGurk et al., 2007a; Fiszdon et al., 2008). Further, although there is some evidence for generalization following restitution-based remediation (see Krabbendam & Aleman, 2003 for a review), accumulating evidence supports a combination of restitution- and strategy-based remediation to facilitate the transfer of cognitive gains to everyday functioning (McGurk & Wykes., 2008). For example, when cognitive remediation is combined with a supportive employment

or work therapy program, the associated benefits may be durable for at least as long as three years (Bell et al., 2005; Greig et al., 2007; McGurk et al., 2007a; Bell et al., 2008): patients enrolled in work therapy with adjunctive cognitive remediation held more jobs, worked more hours, and earned more wages than those patients who did not receive cognitive remediation. If shown to be similarly effective in patients with mood disorders, cognitive remediation programs could be an attractive treatment option for patients with BD or MDD who experience significant, illness-related cognitive deficits and associated functional impairment.

As with any therapeutic intervention, however, not all patients improve following cognitive remediation. In patients with schizophrenia, there are several factors that partially account for this variability in response. For instance, motivational state is recognized as a strong determinant of outcome (Bellack et al., 1999; Barch, 2005; Velligan et al., 2006), as is premorbid intellectual status and extent of cognitive impairment; these latter factors not only predict response to cognitive remediation, but also impact the degree to which cognitive gains generalize beyond the training tasks (e.g., Fiszdon et al., 2006). Factors such as a therapist's educational background and training, the study habits of the patient, and treatment intensity also impact outcome (Medalia & Richardson, 2005). Interestingly, total dosage (i.e., number or duration) of sessions does not appear to be strongly predictive of change (Krabbendam and Aleman, 2003), although presumably there is a minimum dose requirement for the treatment to be effective.

Studies have also shown that positive and negative symptoms have minimal impact on training (Medalia & Richardson, 2005; Kurtz et al., 2009), however cognitive and functional benefits are most pronounced when patients are clinically stable (Wykes et al., 2011). Certain pharmacological treatments may also be an issue; there is some evidence to suggest that typical antipsychotics and anticholinergic medications negatively impact change following remediation in patients with schizophrenia (Vinogradov et al., 2009; Wykes et al., 1999).

In Chapter 3 we examine the efficacy of CACR in a naturalistic sample of patients with mood disorders, and explore several potential predictors of response to remediation. To this end, we administered objective neuropsychological tests and collected subjective ratings of psychosocial functioning at a baseline time-point, immediately following the intervention, and again at a 3-month follow-up visit. To determine factors that predict improvement following a course of cognitive remediation, we examined four potential moderators of change: depressive symptom severity, medication load, degree of cognitive impairment, and motivation. In line with the schizophrenia literature, we expected to see improvements on objective neuropsychological tests immediately following the intervention, and gains were expected to be maintained at a 3-month follow-up visit. We also predicted a positive association between improvement on objective measures of cognitive functioning, and subjectively-assessed psychosocial functioning. We expected depressive symptom severity, medication load, and

cognitive impairment to negatively impact change, and motivation for treatment to be positively associated with improvement.

1.3 Neural correlates of cognitive remediation

Cognitive remediation may be an effective treatment option for patients with neuropsychological deficits; however there is a paucity of work devoted to understanding the neurobiological changes that mediate improvement following this type of intervention. In fact, the translation of neuroplasticity research to clinical therapies has been highlighted as an important avenue for further study (Cramer et al., 2011), as only five papers to date have examined the structural or functional correlates of cognitive training in psychiatric or neurological samples (Wykes, 1998; Wexler et al., 2000; Eack et al., 2010; Laatsch et al., 2004; Kelly et al., 2006). All report evidence of neural change and corresponding behavioural improvements following remediation, however. For example, in eight individuals with schizophrenia, improvements in verbal memory were associated with increased activation in the inferior frontal gyrus (Wexler et al., 2000). Changes in behavioural strategy and accuracy on a verbal fluency task were linked to activation changes in frontal and parietal regions in two patients with schizophrenia (Wykes, 1998). Evidence from a single study that measured *structural* change following remediation in patients with schizophrenia offers convergent support for the neuroprotective effects of remediation; this study found that cognitive enhancement therapy protected against gray matter volume

loss in left medial temporal regions (Eack et al., 2010). Although further research is needed to clarify which brain networks are most amenable to neuroplastic change following remediation—and to determine the specificity and stability of these changes—these findings establish the potential for functional imaging to provide important information about how and where in the brain these treatments exert their effect.

In Chapter 4, we use blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) to explore the neural correlates of cognitive remediation in patients with mood disorders. We measured functional activation during an n-back working memory paradigm and a recollection memory-process dissociation task; i) to compare task activation in the patient sample with activation in a healthy control sample, and ii) to compare task activation in the patient sample prior to and following remediation. We chose to use an n-back paradigm and a recollection memory task because the neural networks involved in working memory and recollection memory task performance are reasonably well understood, particularly in normative populations. For instance, the n-back task reliably activates frontoparietal control networks—regardless of whether the paradigm is verbal, object, or spatial—including medial and lateral prefrontal regions, the frontal poles, and medial and lateral regions of the posterior parietal cortex (see Owen et al., 2005 for a meta-analysis). Recollection memory processes reliably activate medial temporal lobe structures;

notably, anterior regions of the hippocampus and parahippocampal gyrus for episodic and semantic retrieval, and posterior regions of the hippocampus and parahippocampal gyrus for autobiographical retrieval (Burianova & Grady, 2007; Burianova et al., 2010). Studies have also shown a positive association between successful encoding and anterior hippocampal activation (Fairhall et al., 2010).

During n-back task performance, patients with BD and MDD show a broadly similar pattern of activation across frontoparietal control networks compared to healthy controls, although differences in the *extent* of activation between patients and healthy control subjects, particularly within prefrontal regions, are often reported. There is little consensus on the directionality of these differences, however. For instance, with task performance considered, some studies have shown decreased activation in dorsolateral prefrontal cortices in depressed and euthymic patients, relative to healthy control subjects (Garrett et al., 2011; Hamilton et al., 2009; Monks et al., 2004), whereas other studies show *greater* activation in lateral prefrontal regions (Harvey et al., 2005; Matsuo et al., 2007; Fitzgerald et al., 2008). In studies where task performance in the patient group is impaired relative to controls, findings are similarly equivocal; some report attenuated activity in lateral prefrontal regions (Lagopoulos et al., 2007), while others show *hyperactivation* in frontopolar cortex, temporal cortex, and posterior parietal regions (Adler et al., 2004). We therefore expected patients and healthy control subjects to activate a broadly similar network of frontoparietal

control regions with increasing memory load, and we predicted that a direct comparison between the patient group and the healthy control group would show decreased activation in the patient sample in frontal control regions, regardless of task performance (Townsend et al., 2010; Garrett et al., 2011; Hamilton et al., 2009; Thermenos et al., 2010; Monks et al., 2004).

There are relatively few studies examining the neural correlates of recollection memory performance in patients with BD or MDD. Rather, the medial temporal lobe has been examined primarily with structural imaging methods in this patient group. Several independent meta-analyses show smaller hippocampal volumes in patients with MDD, relative to healthy control subjects (Koolschijn et al., 2009; McKinnon et al., 2009; Konarski et al., 2008; Malykhin et al., 2010). Volumetric studies of the hippocampus in patients with BD are less consistent (Geuze et al., 2005; Konarski et al., 2008; Frey et al., 2007), however lithium treatment has been found to *increase* hippocampal volume (Yucel et al., 2007; 2008), which may partially account for these discrepant findings.

Although the functional consequences of hippocampal volume decreases in patients with mood disorders are largely unknown, there is some evidence to suggest that these volume reductions impact memory retrieval. For instance, volume reductions were associated with impaired performance on recollection memory tests in patients with MDD (MacQueen et al., 2003; Kaymak et al., 2010). Another study found a positive association between successful encoding

and anterior hippocampal activation in healthy control subjects, a relation that was not present in patients with MDD (Fairhall et al., 2010). These findings are consistent with our own recent report of decreased hippocampal activation and impaired performance on recollection memory trials in patients with MDD, relative to healthy control subjects (Milne et al., 2011). Thus, on the recollection memory task, we expected that patients and healthy controls would both activate medial temporal lobe regions on recollection memory trials. We predicted attenuated activation in patients, compared to healthy controls.

1.4 Overview of the study

The experimental work presented in this thesis is based on behavioural and functional neuroimaging data collected during a study examining the effectiveness of computer-assisted cognitive remediation in patients with mood disorders. In Chapter 2 we show that neuropsychological differences between patients with BD and MDD are primarily quantitative (i.e., degree of deficit), not qualitative (i.e., pattern of deficit). In Chapter 3 we present the results of our primary analysis, where we show significant improvement on neuropsychological tests of working memory and delayed memory following remediation, as well as significant positive associations between improvement in neuropsychological test performance, and improvement in subjectively-rated cognitive and psychosocial functioning. In Chapter 4 we present evidence of increased activation in frontal control regions during working memory, and in the right hippocampus during

recollection memory. Although behavioural performance on these tasks was stable across visits, the observed increased activation in frontal and medial temporal brain regions following remediation is consistent with gains on neuropsychological tests of working memory and delayed recall following remediation.

Taken together, the results presented in this thesis provide convergent behavioural and neural evidence to demonstrate the efficacy of computer-assisted cognitive remediation for patients with mood disorders. These novel findings contribute to the growing body of literature that shows cognitive remediation to be an effective cognitive management strategy across a range of psychiatric and neurological disorders. Based on our findings, depressive symptom severity and motivation for treatment may be important factors for clinicians to evaluate before recommending cognitive remediation, particularly in considering *when* an intervention might be most effective. On balance, cognitive impairment and medication load appear to have a minimal impact on efficacy. Addressing these deficits early with a standardized treatment plan may prevent or minimize the impact of cognitive deficit on functional outcome and quality of life in these individuals. These programs have the potential to be widely beneficial for patients with mood disorders.

CHAPTER 2

Comparison of the pattern of cognitive deficit in patients with bipolar disorder or major depressive disorder

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Trait-related cognitive deficits are reliably documented in patients with BD and MDD, however further research is needed to determine how these groups compare to each other, in terms of pattern and degree of deficit. We address this issue here with an empirical analysis that contrasts cognitive functioning in patients with BD and MDD directly. We show that patients with BD and MDD differ primarily in degree—not pattern—of deficit. The degree of overlap in pattern of deficit between patients with BD and MDD makes it likely that both groups would benefit from structured remediation programs that emphasize similar areas of cognitive deficit.

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Abstract

Background: Stable cognitive deficits have been reliably documented in both bipolar disorder (BD) and major depressive disorder (MDD), but few studies have compared directly the pattern and degree of cognitive impairment across these patient groups.

Methods: We used standardized neuropsychological tests to characterize the cognitive profile of stable outpatients with primary BD or MDD. The patient groups were matched for illness duration and depressive symptom severity.

Results: Patients with BD and MDD showed deficits on standardized tests of processing speed, speeded set shifting, and working memory; scores from both patient groups fell approximately 0.5 to 1 standard deviation below those of healthy controls. Only patients with BD, however, were impaired on tests of explicit learning and memory and on tests of phonemic fluency.

Limitations: Medication burden was greater in patients with BD than those with MDD. The neuropsychological test battery was limited in scope.

Conclusions: The degree of overlap in cognitive performance observed between patient groups makes it unlikely that profiles of cognitive function will provide a means to differentiate patients with BD from those of MDD in a reliable manner. Those group differences that did emerge may, however, point towards neurobiological processes that differentially affect key brain regions across the mood disorders illness spectrum.

1. Introduction

It can be difficult to differentiate bipolar disorder (BD) from major depressive disorder (MDD); survey data of people with BD found that 69% of respondents had been misdiagnosed at least once, with half of these respondents reporting an incorrect diagnosis of unipolar depression (Hirschfeld et al., 2003). A number of potential approaches aimed at reducing rates of diagnostic error have been proposed, including the use of endophenotypes as an adjunctive tool (Gottesman and Gould, 2003), but the utility of these approaches remains largely unknown.

The possibility of using cognitive endophenotypes as an adjunct for clinical diagnosis has fueled studies that, when taken together, document the presence of stable, state-independent cognitive deficits in patients with BD and MDD (e.g., Kurtz and Gerraty, 2009; Arts et al., 2008; Nakano et al., 2008). Critically, cognitive deficits are also detectable early in the course of illness, and to a lesser extent in first-degree relatives of patients with mood disorders (Bora et al., 2009; Brotman et al., 2009; Sarosi et al., 2008). These findings point towards several cognitive domains as candidate cognitive endophenotypes, particularly for patients with BD, where the majority of criteria for identification of an endophenotype have been satisfied (see MacQueen et al., 2005 for an overview).

It remains to be determined however, whether a patient's neuropsychological profile can actually be used to enhance the likelihood of

differentiating MDD and BD. Relatively few research studies have compared directly the cognitive profile of individuals with BD and MDD (e.g., Bora et al., 2010; Hill et al., 2009), and even fewer have documented this comparison in euthymic or stable patients. Extant data are conflicting: although Paradiso et al. (1997) found that remitted MDD patients were significantly impaired relative to healthy control subjects on measures of attention, memory, and executive functioning, no differences emerged in performance between remitted BD patients and healthy control subjects on these same measures (Paradiso et al., 1997). In another study, however, although memory and executive functioning performance was equivalent in remitted depressed BD and MDD patients, attention and inhibitory control deficits were most pronounced in the remitted patients who had been recently manic (Gruber et al., 2007). A third study (Stoddart et al., 2007) also showed a similar degree of impairment between remitted MDD and remitted BD patients, but further demonstrated that participants with BD exhibited a specific executive deficit independent of attention impairment. Finally, a fourth study found that whereas patients with remitted BD were significantly *more* impaired than patients with remitted MDD on tests of verbal memory, set-shifting, and inhibitory control, patients with MDD were impaired, relative to controls, on a measure of set-shifting only (Smith et al., 2006).

The purpose of the present study was to compare the pattern and degree of cognitive impairment in a large sample of people with BD or MDD. The groups

were matched for illness duration and depressive symptom severity, allowing us to minimize between-group variability in cognitive performance associated with these factors.

2. Methods

2.1 Participants

Patients diagnosed with BD or MDD according to DSM-IV criteria were recruited through the Mood Disorders Clinic at St. Joseph's Healthcare, Hamilton. Age- and gender-matched healthy control subjects with no psychiatric history, based on the *Structured Interview for DSM-IV, Axis I Disorders, Patient version* (SCID-I/P; First et al., 1995) were recruited using newspaper advertisements and flyers. All clinical assessments were completed by trained psychiatric nurses. The protocol was approved by the research ethics board at St. Joseph's Healthcare, Hamilton. After a complete description of the study procedures, written informed consent was obtained from each subject.

2.2 Procedure

Patients and healthy controls with complete clinical and demographic data were included in the present analyses. Patient groups and controls were matched for age, gender, estimated verbal intelligence quotient (estVIQ), and education. The patient groups were also matched for illness duration. Patients and healthy controls completed the Digit Symbol Substitution test (DSS; Wechsler, 1997), the Trail Making Test A and B (TMT-A & B; Reitan and Wolfson, 1985), and the

Controlled Oral Word Association Test, letters *F*, *A*, and *S* (COWAT; Benton et al., 1983). A subset of patients and healthy controls completed the Digit Span forward and backward (DS; Wechsler, 1997), and the Hopkins Verbal Learning Test (HVLT; Brant and Benedict, 2001). Depressive symptom severity was assessed using the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960), and manic symptom severity was assessed using the Young Mania Rating Scale (YMRS; Young et al., 1978).

2.3 Medication Load

Following Almeida et al. (2009) and Versace et al. (2008), we categorized antidepressant medications and mood stabilizers into low (1)- or high (2)-dose groupings (Sackeim, 2001). Antipsychotic medications were converted to chlorpromazine hydrochloride dose equivalents according to the following: 0 (no medication), 1 (equal to or below the chlorpromazine dose equivalent), or 2 (above the chlorpromazine dose equivalent), relative to the mean effective daily dose of chlorpromazine (150 mg; Davis and Chen, 2004). A composite index of medication load was calculated by summing together the medication codes in each medication category, for each participant.

2.4 Statistical Analyses

Statistical analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago IL). Differences between groups were assessed using the Student's *t* -test or a one-way analysis of covariance (ANCOVA), in the case of normal

distribution, and with the non-parametric Mann-Whitney or Kruskal-Wallis test when there were significant deviations from normality. The significance threshold for all tests was set at $p \leq 0.05$. Raw neuropsychological test scores were converted to age-adjusted, or age- and education-adjusted T scores where possible. Group comparisons were performed on individual neuropsychological test to examine differences in performance between healthy controls, patients with MDD, and patients with BD. HRSD scores were entered into each ANCOVA as a covariate to account for residual mood symptoms. Finally, to determine the extent to which medication burden influenced performance, we calculated Pearson product-moment correlation coefficients between neuropsychological test scores and medication load.

3. Results

In total, 171 subjects were assessed: 60 patients with BD, 52 patients with MDD and 59 healthy controls. See Table 1 for a demographic summary and Table 2 for a summary of neuropsychological test scores.

Processing Speed. There was a main effect of group on the DSS, F (2, 146) = 5.23, p = .01. Healthy controls performed better than both BD (p < .01) and MDD (p = .03) patients.

Table 1: Demographic data

	BD *n = 50* mean (SD)	*MDD* *n = 50* mean (SD)	*Control* *n = 50* mean (SD)	*Test Statistic*	*p*
Age (years)	43.9 (8.2)	43.9 (11.1)	43.0 (11.2)	0.1[a]	.87
Sex Ratio (M:F)	12:38	17:33	15:35	1.2[b]	.54
Education (years)	14.9 (2.8)	15.2 (3.3)	15.4 (2.7)	0.3[d]	.71
NART-estVIQ	111.7 (8.1)	108.3 (9.2)	111.7 (10.2)	2.1[d]	.13
HRSD-17	11.9 (6.3)	11.9 (5.8)	1.8 (2.3)	0[c]	1
YMRS	0.9 (1.8)	0.4 (1.0)	0.1 (0.5)	1.7[c]	.09
Duration Ill (years)	20.8 (9.2)	19.6 (12.8)	---	0.5[c]	.60
Total months ill	95.3 (58.4)	64.7 (62.5)	---	3.3[c]	.08
Medication Load	3.7 (1.7)	1.9 (1.4)	---	24.4[c]	<.01*

	BD *n = 24* mean (SD)	*MDD* *n = 30* mean (SD)	*Control* *n = 24* mean (SD)	*Test Statistic*	*p*
Age (years)	49.3 (8.0)	47.4 (8.5)	43.1 (12.8)	2.8[a]	.25
Sex Ratio (M:F)	4:20	7:23	8:16	1.8[b]	.40
Education (years)	15.4 (3.6)	15.7 (3.1)	16.5 (3.5)	0.7[d]	.50
NART-estVIQ	107.9 (8.9)	108.1 (9.1)	111.1 (6.8)	0.9[d]	.40
HRSD-17	9.4 (5.8)	10.3 (5.0)	2.2 (2.8)	-0.6[c]	.53
YMRS	1.5 (2.1)	0.3 (0.7)	0.2 (0.7)	2.7[c]	.01*
Duration Ill (years)	27.3 (10.7)	23.9 (13.8)	---	1.1[c]	.30
Total months ill	61.6 (46.0)	67.1 (67.3)	---	0.1[c]	.85
Medication Load	4.8 (1.4)	1.9 (1.5)	---	49.8[c]	<.01*

BD = bipolar disorder; MDD = major depressive disorder; NART-estVIQ = National Adult Reading Test estimated verbal intelligence quotient; HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale

[a] Kruskal-Wallis test

[b] Pearson's Chi-Squared test

[c] Student's *t* test

[d] *F* test

Table 2: Neuropsychological test scores

	BD *n = 50* mean (SD)	*MDD* *n = 50* mean (SD)	*Control* *n = 50* mean (SD)	*F*	*p*
Processing Speed					
DSS – agescaled score	10.1 (2.6)	10.5 (2.5)	12.5 (2.5)	5.2	.01*
Simple Attention					
TMT-A T score	43.5 (9.8)	45.0 (11.7)	48.6 (8.1)	1.3	*Ns*
Executive Functioning					
COWAT T score	46.3 (10.0)	49.2 (11.7)	52.5 (10.8)	3.4	.03*
TMT-B T score	48.0 (10.7)	48.2 (11.6)	54.4 (9.5)	4.5	.01*
	BD *n = 24* mean (SD)	*MDD* *n = 30* mean (SD)	*Control* *n = 24* mean (SD)	*F*	*p*
Explicit Memory (HVLT)					
Delayed recall T score	35.8 (12.3)	41.7 (11.0)	45.2 (11.5)	3.1	.05*
Simple Attention					
DS Forward	7.3 (2.3)	7.9 (2.4)	8.9 (2.0)	1.0	*Ns*
Working Memory					
DS Backward	6.1 (1.6)	6.3 (1.9)	8.2 (2.7)	5.9	<.01*

BD = bipolar disorder; MDD = major depressive disorder; DSS = Digit Symbol subtest; TMT-A = Trail Making Test part A; COWAT = Controlled Oral Word Association; TMT-B = Trail Making Test part B; HVLT = Hopkin's Verbal Learning Test; DS = Digit Span; *ns* = not significant

Simple Attention. There were no significant group differences in performance on the TMT-A. There were no significant group differences in performance on the DS Forward.

Explicit Memory. There was a main effect of group for delayed recall on the HVLT, F (2, 73) = 3.05, p = .05. Healthy controls outperformed BD patients (p = .03). MDD patients outperformed BD patients at the level of a trend (p = .06).

Executive Functions–fluency, set-shifting. There was a main effect of group on the COWAT, F (2, 146) = 3.44, p = .03. Healthy controls generated significantly more words than patients with BD (p = .02), and patients with MDD performed at a level intermediate to the two groups (p's > .05). There was a main effect of group on the TMT-B, F (2, 146) = 4.52, p = .01. Healthy controls were significantly faster than both BD patients (p < .01) and MDD patients (p = .02).

Working Memory. There was a main effect of group on the DS Backward, F (2, 74) = 5.93, p < .01. Both patient groups performed poorly compared to controls (p's = .02 and .01 for BD and MDD, respectively).

Medication Effects. Only the association between delayed recall and medication load was significant, r = -.34, p = .01; patients with higher medication loads had lower delayed recall scores.

4. Discussion

Deficits in processing speed, speeded set-shifting, and working memory are present in patients with BD and MDD and cannot be accounted for by the presence of residual mood symptoms. Whereas the performance level of patients with BD fell approximately 1 standard deviation below that of healthy controls on neuropsychological tests tapping these domains, the performance of patients with MDD was approximately 0.5 to 0.75 of a standard deviation lower than that of healthy controls. There were no significant differences in the performance of patients with BD compared to those with MDD on these measures, despite the fact that the sample size was large and should have had the ability to detect any clinically significant differences between the groups. These results parallel Stoddart and colleagues' (2007) finding that BD and MDD patient samples were similarly impaired on measures of attention and executive functioning relative to healthy controls, and are in line with the observation that performance differences between BD and MDD patients in domains of attention and executive function may be primarily quantitative (i.e., degree of deficit), and not qualitative (i.e., pattern of deficit) (Stoddart et al., 2007).

In fact, Stoddart and colleagues (2007) found only one difference between BD and MDD patients in the domain of executive functioning: patients with BD exhibited a specific executive deficit on the Hayling Sentence Completion Test (Burgess and Shallice, 1997), a measure of the ability to successfully inhibit

appropriate responses. In our sample, only patients with BD had measurable deficits in verbal fluency, scoring approximately 1 standard deviation lower than healthy controls. In these two studies, the only executive impairment specific to BD patients was observed on tasks that rely, to a large extent, on word generation abilities mediated by prefrontal regions. Consistent with these findings, a review of studies examining fluency performance in patients with MDD reported that deficits in this domain were state-dependent; clinical recovery was associated with normalization of verbal fluency performance (Douglas and Porter, 2009).

On tests of explicit memory, patients with BD again performed at a level approximately 1 standard deviation lower than that of controls. The presence of learning and memory deficits in patients with BD have been consistently reported in symptomatic *and* euthymic BD samples (see Kurtz and Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009 for reviews and meta-analyses). Performance of MDD patients was intermediate to that of BD patients and healthy controls; it was not significantly different from either group. A review of cognitive functioning in MDD patients found that verbal learning and memory deficits were among the domains *most* sensitive to clinical state: improvement in mood was associated with improvement in verbal learning and memory performance (Douglas and Porter, 2009). Thus, learning and memory deficits in MDD patients may be state-dependent, particularly subtle, or restricted

to a subgroup of patients such as those with extensive illness burden (e.g., MacQueen et al., 2002).

There was a significant association between verbal delayed recall performance and medication load, such that patients with a higher medication burden had lower scores on this task. This is in contrast with a recent meta-analysis that found medication effects only in the domain of processing speed in patients with BD (Bora et al., 2009). Few studies have directly examined the impact of polypharmacy on cognition in patients with mood disorders, however.

There are several limitations to this study. Patients with BD had a significantly higher medication burden than patients with MDD. The extent to which the observed decrements in patients with BD were due to medication effects remains to be addressed. A second limitation of the present study is the limited neuropsychological test battery. More comprehensive test batteries could better delineate subtle differences in the pattern of deficits between the two groups.

These findings confirm that there are differences in cognitive function between patients with MDD and BD, but these differences appear to be primarily in degree, and not pattern of deficit. The reasons why patients with BD tend to have a greater degree of impairment than those with MDD, particularly in domains of verbal fluency and verbal memory, remain to be clarified and may point to important neurobiological differences between these illnesses. It appears

unlikely, however, that standard neuropsychological measures can be reliably used as an adjunctive tool to reduce diagnostic uncertainty in patients with BD or MDD.

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CHAPTER 3

A controlled trial of cognitive remediation on cognition and quality of life in patients with mood disorders

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Here we present the results of a 10-week trial of cognitive remediation for patients with mood disorders, thus extending extant findings of short-term cognitive improvement following training in this patient group. We show gains to domains of memory, and to perceived level of functioning. We also show that severity of cognitive impairment and medication load are not barriers to successful response; thus, cognitive remediation has the potential to be widely beneficial for patients who experience cognitive dysfunction associated with a primary mood disorder.

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Abstract

Objective: Mood disorders are associated with impairment in cognitive performance across multiple domains. Cognitive remediation has been successfully implemented for patients with schizophrenia, but few studies have explored the potential efficacy of remediation in patients with mood disorders.

Methods: We examined the effect of 10 weeks of computerized cognitive remediation in patients with mood disorders, on measures of neuropsychological and psychosocial functioning.

Results: Participants improved on measures of working memory and delayed recall following treatment. There were positive correlations between improved cognitive functioning and psychosocial functioning. Depressive symptom severity and engagement in treatment were predictive of improvement. Neither medication burden nor severity of cognitive impairment predicted response.

Conclusions: Computerized cognitive remediation is associated with sustained improvements in cognitive and psychosocial functioning in patients with mood disorders. It is simple, accessible, and does not require extensive supervision. Cognitive remediation has the potential to be widely beneficial for patients with mood disorders.

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Introduction

State-independent cognitive deficits are apparent in patients with bipolar disorder[1] (BD) and major depressive disorder[2,3] (MDD), however there is a lack of research focused on how to manage this component of the illness. Cognitive remediation, which has been studied extensively in patients with schizophrenia, is one such treatment option. In particular, computer-assisted cognitive remediation (CACR) shows beneficial effects to attention, processing speed, and memory[4]. Preliminary studies of CACR for patients with mood disorders also show benefits[5,6], but the question of whether these effects extend beyond short-term improvement on objective neuropsychological tests remains to be addressed.

The present study had several objectives, aimed at extending these extant findings in patients with mood disorders. We evaluated the efficacy of a 10-week restitution-based CACR program using measures of neuropsychological and psychosocial functioning. We assessed participants at baseline, immediately following the intervention, and again after 3-months to determine whether gains were maintained following cessation of the formal intervention. A further objective of the current study was to identify factors associated with response to training. Several moderators of cognitive change have been identified in patients with psychotic disorders including motivation, treatment intensity, therapist training[7], cognitive impairment[8], and concurrent medication use[9,10]. We expanded the primary treatment sample to include patients previously trained on the same

CACR method[6], and examined the influence of depressive symptom severity, medication load, cognitive impairment, and motivation on treatment response in this combined patient group.

Methods

Patients diagnosed with a primary mood disorder were recruited through the Mood Disorders Clinic at St. Joseph's Healthcare to participate in a study examining the effectiveness of a 10-week CACR program. Healthy control subjects with no psychiatric history were recruited using newspaper advertisements and flyers. The protocol was approved by the research ethics board at St. Joseph's Healthcare. After a complete description of study procedures, written informed consent was obtained. In total, 101 subjects consented to participate.

Patients were eligible if they had a confirmed primary diagnosis of BD or MDD, according to the *Structured Interview for DSM-IV, Axis I Disorders, Patient version*[11] (SCID-I/P), were euthymic or had stable subsyndromal symptoms at baseline assessment, were between 18 – 60 years of age, and were able to provide written informed consent. Healthy control subjects had no history of psychiatric illness, as assessed with the SCID-I/P[11]. Exclusion criteria included: treatment with anticholinergic or typical antipsychotic medication, electroconvulsive therapy or transcranial magnetic stimulation within the past

year, a lifetime history of substance dependence or substance abuse within the past year, a history within the past year of an endocrine or other medical disorder known to adversely affect cognition (e.g., Cushing's, uncontrolled diabetes, seizure disorder), and English comprehension lower than a grade 6 level.

Study Design

Mood symptoms, neuropsychological, and psychosocial functioning were assessed at baseline (PRE), following the completion of the remediation program (POST), and at a six-month (relative to baseline) follow-up visit (FLW-UP). Twelve patients with BD and 28 patients with MDD completed the study. A group of 18 healthy control subjects participated in the same assessment battery at corresponding PRE, POST, and FLW-UP visits to control for test-retest effects in the patients.

An additional 12 patients from a pilot study of CACR in MDD were added to the primary sample to examine the effect of moderator variables on treatment response. The pilot study used the same CACR program[12] and a similar assessment battery at PRE and POST[6].

Assessment. Depressive and manic symptoms were assessed using the Hamilton Rating Scale for Depression[13] (HRSD) and the Young Mania Rating Scale[14] (YMS). Estimated premorbid verbal IQ (estVIQ) was assessed with the National Adult Reading Test[15,16] (NART). Attention was assessed using the Wechsler Adult Intelligence Scale – Revised[17] (WAIS-R) Digit Span Forward

(DS-F), the Trail Making Test – Part A[18] (TMT-A), and the accuracy indices from Ruff's 2 & 7 Selective Attention Test[19]. Processing speed was assessed using the WAIS-R Digit Symbol subtest[17] (DSS), and the speed indices from Ruff's 2 & 7 Selective Attention Test[19]. Learning and memory were assessed using the Hopkin's Verbal Learning Test-Revised[20] (HVLT). The executive functions assessed were: phonetic and semantic fluency[21] (COWAT) and mental flexibility[18] (TMT-B). Working memory was assessed with the WAIS-R Digit Span Backward[17] (DS-B).

Subjective reports of cognitive and psychosocial functioning were collected using the Medical Outcomes Study 36-item Short Form Health Survey[22] (SF-36), the Life Skills Profile[23] (LSP), and the Quality of Life Enjoyment and Satisfaction Questionnaire[24] (Q-LES-Q).

***Computer-Assisted Cognitive Remediation* (*CACR*).** This intervention consisted of 20 computer tasks from PSSCogRehab[12] aimed at improving performance in domains typically affected in BD and MDD: speed, attention, verbal memory and executive function. Training was hierarchically organized, with successful completion of one module required before beginning a new module. The difficulty level of each task was modified according to each subject's individual abilities. Patients trained in one hour sessions, three times a week for ten weeks. All training took place at the Center for Mountain Health Services at

St. Joseph's Healthcare on an outpatient basis. Satisfaction with the intervention was assessed with a questionnaire tailored to the particular protocol.

Statistical Analyses

Statistical analyses were carried out using R version 2.9.2[25]. Demographic and clinical comparisons were made using the Student's *t* -test or a one-way analysis of covariance (ANCOVA) in the case of normal distribution, and with non-parametric tests (Mann-Whitney or Kruskal-Wallis) when there were significant deviations from normality.

To evaluate the efficacy of CACR in the primary sample, a series of mixed effects models were considered for each neuropsychological test. The models included fixed effects for group, time, and a group-by-time interaction (healthy control = reference), and random effects for participants. The 29-item HRSD scores corresponding to the appropriate assessment period (PRE/POST/FLW-UP) were added into the model as covariates.

To examine change in psychosocial functioning following remediation in the primary sample, correlational analyses were performed between an overall measure of cognitive improvement (an average of the standardized change scores for each neuropsychological test; change scores were standardized to those of the control sample), and change scores on three relevant subscales of the psychosocial questionnaires: the cognitive functioning subscale on the SF-36, to assess frequency, severity, and type of cognitive difficulties; the social contact subscale

on the LSP-36, to assess involvement in social activities; and the subjective feelings subscale on the Q-LES-Q, to assess overall level of functioning. We compared the FLW-UP visit to the PRE visit, because gains in neuropsychological functioning were greatest at the FLW-UP visit.

We used the combined patient sample to explore the relative influence of illness factors, cognitive impairment, and motivation for treatment on change in neuropsychological test performance following remediation. To minimize the number of comparisons, we combined standardized change scores (POST-PRE) on tests of attention and processing speed into one category reflecting "information processing" demands, and memory and executive functioning into one category reflecting "information capacity" demands. We then constructed two multiple regression analyses using stepwise entry: the dependent variable in the first regression was information processing change score; information capacity change score was the dependent variable in the second. 29-item HRSD score and medication load at PRE were entered in the first step of each regression as an index of overall "illness burden". To index cognitive impairment at baseline, an average T score for all neuropsychological tests was entered into the model in the second step. A score based on task completion during the intervention was entered into the model in the third step as an index of motivation. Alpha was set at .05 for all analyses.

Medication Load. We categorized antidepressant medications and mood stabilizers into low- or high-dose groupings[26-28], and atypical antipsychotic medications were converted to chlorpromazine dose equivalents, relative to the mean effective daily dose of chlorpromazine[29] (150 mg). A composite index of medication load was then calculated for each participant.

Motivation. Previous work has indexed motivation using attendance[7], however our patients were given the option of completing three, 1-hour sessions, or two, 1.5-hour sessions each week; thus, attendance was not consistent across subjects. To quantify motivation, we calculated an index of effort or engagement; namely, the number of tasks completed, versus the number attempted, relative to the total number of tasks required for completion of the program.

Results

Intervention Efficacy - Primary Sample

Intent to Treat. We compared the demographic and clinical characteristics of individuals who dropped from the study (n = 31) and those who completed the study (n = 58). There were no significant differences in age, sex ratio, level of education, or verbal IQ, nor were there any differences in depressive symptom severity or duration of illness. The relative number of individuals with BD who dropped from the study was significantly higher ($X^2 = 4.69$, $p = .03$) than the

proportion of individuals with MDD or healthy controls who dropped from the study.

Demographic and Clinical Data. For the purpose of ensuring adequate exposure to training, participants who attended fewer than 60% of sessions and/or attempted less than 60% of the program were excluded from the primary analysis (n = 10). Demographic and clinical data for the primary sample are reported in Table 1. There were no significant differences in age, years of education, or verbal IQ between patients or healthy controls; there was, however, a significant difference in sex ratio between the patient group and controls ($p < .01$). There were no significant changes in HRSD score or YMS score across the PRE, POST, and FLW-UP visits.

Table 1: Demographic and clinical information for the primary sample

	Patients	*Controls*	
	n = 30	n = 18	
	mean (SD)	mean (SD)	p
Age	49.9 (7.9)	44.5 (12.3)	0.22
Sex ratio	5 M : 25 F	7 M : 11 F	<0.01*
Diagnosis	7 BD : 23 MDD	---	---
Education (years)	16.3 (3.2)	17.4 (3.4)	0.26
NART-estVIQ	111.0 (7.8)	111.8 (6.6)	0.72
17-item HRSD (PRE)	9.2 (5.5)	1.7 (2.7)	---
Illness duration (years)	21.6 (13.7)	---	---
Medication load	2.6 (1.7)	---	---

Eleven patients had at least one other Axis I disorder, including: posttraumatic stress (6), social phobia (3), generalized anxiety (3), panic (2), specific phobia (2), obsessive-compulsive (1), dysthymia (2), binge eating (1), and past alcohol abuse (4). Four patients had been remotely treated with electroconvulsive therapy, and one with transcranial magnetic stimulation.

The average number of cognitive remediation sessions attended was 21.0 (SD=5.3), and the average number of hours completed was 25.0 (SD=5.5). All participants attempted at least 18 of the 20 tasks, and, on average, reached goal criterion on 75% of tasks. Neuropsychological test scores are reported in Table 2, and are organized according to cognitive domain.

Neuropsychological Tests. On the delayed recall portion of the HVLT the remediation group showed improvement relative to stable performance in the control sample. This effect did not reach significance between PRE and POST, however by the FLW-UP visit the degree of change in the remediation sample was significantly greater than that of the control sample ($p = .03$; Figure 1). The remediation group also improved, relative to stable performance in the control group, on the DS-B—a test of working memory—from PRE to POST ($p < .01$), and at the FLW-UP visit ($p < .01$; Figure 1). There was no evidence of relative improvement in the remediation group on neuropsychological tests of attention, processing speed, immediate recall/learning, or executive functioning.

Table 2: Quantitative results for the primary sample: mean difference between healthy controls and the remediation group in change from baseline

	REMEDIATION PERIOD			FOLLOW-UP PERIOD		
	Mean difference	*95% CI*	*p*	*Mean difference*	*95% CI*	*P*
Arousal and Processing Speed						
DSS – age-scaled	0.53	-0.51, 1.58	0.31	0.13	-0.93, 1.19	0.82
TMT-A T-score	-6.83	-13.39, -0.24	0.05*	-2.67	-9.45, 4.11	0.44
Simple Attention						
DS Forward raw score	-0.87	-2.16, 0.42	0.19	-0.94	-2.27, 0.39	0.17
Executive Functioning						
Phonemic (fluency) T-score	-0.24	-5.30, 4.12	0.93	1.09	-4.18, 6.36	0.69
Animal (fluency) T-score	1.37	-6.27, 9.01	0.73	-0.95	-8.83, 6.93	0.81
TMT-B T-score	-1.42	-6.79, 3.95	0.61	-5.31	-10.86, 0.24	0.06
DS Backward raw score	2.31	1.09, 3.53	0.004*	2.55	1.30, 3.80	0.0001*
Explicit Learning (HVLT)						
Total Recall T-score	-0.33	-3.28, 2.62	0.91	0.79	-2.27, 3.85	0.80
Explicit Memory (HVLT)						
Delayed Recall T-score	2.24	-3.76, 8.24	0.47	7.08	0.85, 13.31	0.03*
Selective Attention (Ruff 2 & 7)						
Total Speed T-score	-0.84	-4.31, 2.63	0.63	-3.29	-6.88, 0.30	0.08
Total Accuracy T-score	0.39	-3.20, 3.98	0.83	-0.47	-4.15, 3.21	0.81

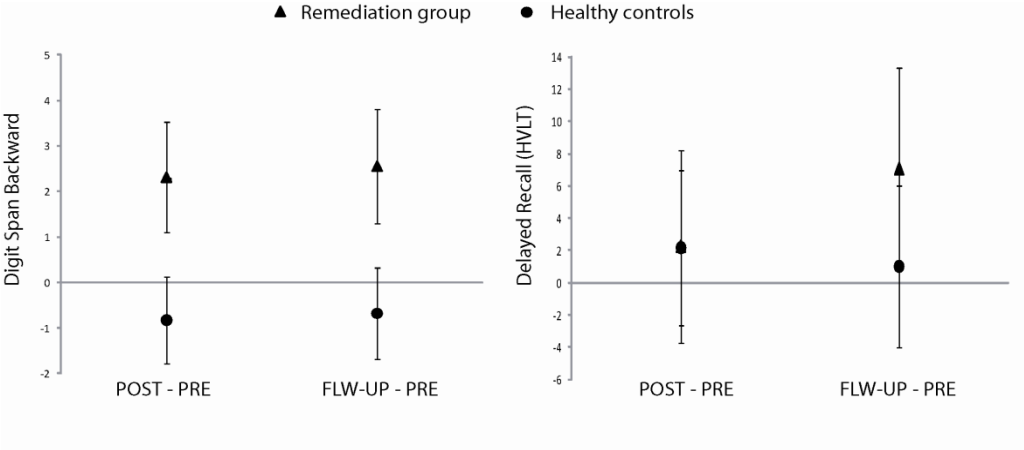

Figure 1. Mean change from baseline and 95% CI on the DS backward (working memory) and HVLT (delayed recall), in the remediation group and healthy control subjects

Psychosocial Ratings. Improvements on the Q-LES-Q subjective feelings subscale were significantly associated with overall improvement in cognition (r = 0.50, p = .01); there were no other significant effects. To further clarify this association, we calculated the standardized change score for each domain of cognitive functioning and measured the relation between each cognitive domain, and the three psychosocial subscales. There was a significant correlation (r = 0.40, p = .03) between improvements on neuropsychological tests of memory, and improved self-reported cognitive functioning on the SF-36. Improvements in executive functioning were associated with improved social well-being on the LSP (r = 0.40, p = .03). Finally, increases on the Q-LES-Q subjective feelings subscale were associated with gains in memory (r = 0.38, p = .04) and attention (r = 0.37, p = .05).

Satisfaction with Treatment. Participants were asked to rate, on a scale of 1 (not at all) to 10 (very much), their subjective experiences of change following the intervention in: reading ability, numerical ability, attention and memory, and organizational skills. Changes in attention and memory were most frequently reported (M = 6.5, SD = 2.1), followed by improvements in numerical abilities (M = 6.3, SD = 2.2), and improvements in organizational skills (M = 6.0, SD = 2.1). In terms of overall satisfaction, all participants in the program rated themselves as either mostly satisfied, or very satisfied with the intervention, and when asked if they would recommend this program to a friend, all but three indicated "yes".

Moderators of Improvement – Combined Patient Group

Demographic and clinical data for the larger sample of patients included in the moderator analysis is reported in Table 3. The regression of illness burden (step 1), cognitive impairment (step 2), and motivation (step 3) on change in information processing (attention and processing speed) is presented in Table 4a; the same regression on change in information capacity (memory and executive functioning) is presented in Table 4b.

Illness burden, particularly depressive symptom severity at baseline, was the best predictor of improvement on tests of attention and processing speed. Illness burden accounted for 20% of the variance in the dependent variable; degree of cognitive impairment and percentage of tasks completed accounted for

an additional 2-3% of variance only. Notably, the relation between these two factors was positive: higher symptom severity at baseline translated to larger gains in information processing. To ensure these improvements were not better explained by concomitant improvements in mood, we constructed another multiple regression model; 29-item HRSD change score (POST-PRE) was entered into the model first, and our index of illness burden (baseline 29-item HRSD

Table 3: Demographic and clinical data for the expanded sample

	mean (SD)
Age	49.3 (7.6)
Sex ratio	13 M : 40 F
Diagnosis	13 BD / 40 MDD
Education (years)	15.6 (3.1)
NART-estVIQ	111.1 (9.5)
T score (average across all tests at baseline)	46.1 (7.0)
29-item HRSD (baseline)	15.9 (9.6)
Illness duration (years)	20.4 (12.4)
Medication load	3.1 (1.9)
Sessions attended	20.1 (5.3)
Tasks completed (%)	70 (20)

score and medication load) was entered second. Change in mood over the course of treatment was not a significant predictor of improvements in information processing, $R^2 = .01$, $F\ (1, 48) = .84$, $p = .36$, and in fact only accounted for approximately 1% of the variance. When baseline 29-item HRSD score and medication load were added in the second step, the overall model was significant, $R^2 = .18$, $F\ (3, 34) = 3.7$, $p = .02$, accounting for an additional 17% of variance.

In the information capacity domain, the only significant predictor of improvement was motivation. Illness burden and cognitive impairment accounted for only 4-6% of the variance in the dependent variable; when our index of motivation was added into the model in the third step, an additional 10% of variance was explained and the overall model was significant.

Discussion

The primary objective of the present study was to evaluate the efficacy of a 10-week CACR program in a naturalistic sample of patients with mood disorders. We found improvements on measures of verbal working memory and delayed recall that were robust three months following treatment completion. We also found positive correlations between changes in cognitive and psychosocial functioning.

Table 4: Quantitative results of the regression analyses in the expanded sample

	β	*95% CI*	*p*
Outcome: information processing change score			
Step 1 [a]			
29-item HRSD score	.02	.01, .03	.01*
Medication load	.04	.01, .07	.15
Step 2 [b]			
29-item HRSD score	.03	.02, .04	.003*
Medication load	.06	.03, .09	.06
Cognitive functioning (PRE)	.02	.01, .03	.12
Step 3 [c]			
29-item HRSD score	.03	.02, .04	.002*
Medication load	.05	.02, .08	.09
Cognitive functioning (PRE)	.02	.01, .03	.10
% tasks completed	-.35	-.79, .09	.43
Outcome: information capacity change score			
Step 1 [d]			
29-item HRSD score	.02	.01, .03	.08
Medication load	.04	-.01, .09	.48
Step 2 [e]			
29-item HRSD score	.02	.01, .03	.08
Medication load	.04	-.01, .09	.44
Cognitive functioning (PRE)	.01	-.02, .03	.71
Step 3 [f]			
29-item HRSD score	.02	.01, .03	.11
Medication load	.06	.01, .11	.25
Cognitive functioning (PRE)	-.03	-.05, -.01	.16
% tasks completed	1.49	.87, 2.11	.02*

[a] $R^2 = .20$, F (2, 35) = 5.5, $p = .01$
[b] $R^2 = .23$, F (3, 34) = 4.7, $p = .01$
[c] $R^2 = .22$, F (4, 33) = 3.6, $p = .01$
[d] $R^2 = .06$, F (2, 38) = 2.3, $p = .11$
[e] $R^2 = .04$, F (3, 37) = 1.6, $p = .21$
[f] $R^2 = .15$, F (4, 36) = 2.8, $p = .04$

Cognitive remediation had the strongest effect in the memory domain; participants showed sustained performance gains relative to stable performance in healthy controls with repeat neuropsychological testing. Conversely, with practice effects considered, performance was stable on tests of simple attention and processing speed, and in two executive domains: fluency and flexibility. A similar pattern of results was reported by Naismith et al.[5]; this preliminary study of cognitive training in patients with mood disorders found improvements on tests of verbal delayed recall, but no benefits to simple attention, processing speed, mental flexibility, or fluency.

Cognitive remediation also produced improvement in patients' subjective assessments of functioning, evidence for some degree of generalization following restitution-based CACR. Subjectively-experienced improvements may further enhance motivation, self-confidence, and feelings of efficacy[30,31], and thus may be essential intermediaries to overt change in psychosocial functioning.

A second objective was to examine clinical factors associated with improvement following CACR. We found that greater motivation was most predictive of improvements in information capacity, whereas higher depressive symptom severity at commencement of the intervention was most predictive of improvements in information processing. Neither medication load nor baseline severity of cognitive impairment predicted response to treatment.

Expectedly, engagement in the intervention predicted improvement. Motivation is a key element in learning and skill development, and motivational state is recognized as an important determinant of outcome in patients with schizophrenia[7,32], so much so that Medalia & Freilich[33] developed a cognitive remediation program that integrates the concept of intrinsic motivation into its approach (Neuropsychological Educational Approach to Remediation; NEAR). Whether motivation for treatment can be enhanced in a systematic way in patients with mood disorders remains to be addressed but may be an important issue to consider, particularly if cognitive remediation programs are implemented with more severely ill patients.

Interestingly, patients with more depressive symptoms were more likely to improve on tasks of attention and processing speed. This effect was not attributable to concomitant improvements in mood that occurred over the course of treatment, or to differences in cognitive functioning associated with depressive symptom severity. One possible interpretation is that individuals with more severe depressive symptoms showed a more pronounced response to the nonspecific effects of stimulation associated with any intervention (e.g., novel social interactions, behavioural activation). Our sample was comprised of outpatients with subthreshold symptom levels, however; patients with full threshold illness severity might *not* be more likely to benefit than those with lower grade symptoms.

Cognitive impairment had little impact on change in neuropsychological performance. This has also been reported in schizophrenia-spectrum disorders, where even the most impaired patients show gains in cognitive functioning following training[8,34]. In another study, BD patients with more pronounced cognitive impairment showed weaker gains on psychosocial and occupational indices following cognitive behavioural therapy combined with strategy-based remediation[35]. Thus, cognitive impairment may not impact training performance *per se*, but may affect the degree to which a patient can extend specific cognitive gains to novel, untrained tasks and real-world situations.

In summary, these findings support the efficacy of CACR for patients with mood disorders, particularly in domains of delayed recall and working memory. Participants' perception of functioning also improved measurably with CACR. Motivation for treatment may be important to assess before recommending cognitive remediation. On balance, severity of cognitive impairment and medication load are not barriers to successful response, at least within the range of patients assessed here. CACR, which is simple and relatively inexpensive to offer, has the potential to be widely beneficial for patients who experience cognitive dysfunction associated with a primary mood disorder.

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CHAPTER 4

Neural correlates of cognitive remediation in patients with mood disorders

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Here, we explore the potential for neuroplastic change within memory networks following a course of cognitive remediation—an area of research that has received little attention to date. We confirm the expected pattern of task-related functional abnormality across frontal and temporal memory networks in a large sample of patients diagnosed with a primary mood disorder, and we show significant increases in activation post-remediation within these networks. These results provide some of the first evidence for functional change following cognitive remediation in patients with mood disorders.

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Abstract

Context: Cognitive remediation may be an effective strategy for patients with neuropsychological deficits; there is, however, a paucity of work devoted to understanding the neurobiological changes that mediate improvement following this type of intervention.

Objective: To examine the neural correlates of working memory and recollection memory in a sample of patients with mood disorders, before and after cognitive remediation. We also compared functional activation in the patient sample at baseline with activation in a healthy control sample on the same tasks.

Design: Patients underwent functional imaging scans before and after the 10-week cognitive remediation intervention.

Setting: A mood disorders outpatient clinic at a university-affiliated medical center.

Patients: Patients with a primary mood disorder who were euthymic or had stable subsyndromal symptoms.

Intervention: Patients trained for three hours a week for ten weeks using a restitution-based computer-assisted cognitive remediation program. The cognitive domains trained were: selective attention, working memory, executive function, sensorimotor skills, declarative memory, and problem solving.

Main Outcome Measure: We used blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) during an n-back working memory paradigm and a recollection memory task.

Results: Patients improved significantly on behavioral tests of memory following training. There was increased activation on the n-back task in regions of lateral and medial prefrontal cortex, and in the dorsal cingulate following remediation. There was increased activation in the right hippocampus during the recollection memory task following remediation.

Conclusions: These results provide some of the first evidence that cognitive remediation can result in neuroplastic change in lateral and medial prefrontal regions that support working memory, and in medial temporal regions that subserve recollection memory.

Introduction

Cognitive remediation may be an effective strategy for patients with neuropsychological deficits;[1, 2] there is, however, a paucity of work devoted to understanding the neurobiological changes that mediate improvement following training. To date, five studies have examined the structural and functional correlates of cognitive training across a variety of psychiatric and neurological conditions.[3-7] All have reported changes in brain activity in association with behavioural improvements following remediation.

Deficits in working memory and recollection memory are frequently reported in patients with mood disorders,[8-10] and imaging studies comparing patients to healthy controls on working memory and recollection memory tasks have identified key structural and functional alterations in the neural substrates that subserve performance on these tasks. For example, functional imaging studies of working memory often show attenuated activation in patients, compared to healthy controls, particularly within lateral prefrontal regions.[11-14] Deficits in recollection memory performance in patients with mood disorders have been linked to decreased hippocampal activation,[15] and to smaller hippocampal volumes.[16, 17] To date, however, no studies have explored the potential for change within these memory networks following cognitive remediation in patients with mood disorders.

Accordingly, the primary aim of the present study was to examine the neural correlates of working memory and recollection memory in a sample of patients with BD and MDD, before and after a computer-assisted cognitive remediation program (CACR). We used functional magnetic resonance imaging (fMRI) to measure neural activation during an n-back working memory paradigm and a recollection memory task. Patients also completed neuropsychological tests of working memory and delayed recall, before and after remediation.

Methods

Participants

Patients diagnosed with a primary mood disorder according to DSM-IV criteria were recruited through the Mood Disorders Clinic at St. Joseph's Healthcare to participate in a study examining the effectiveness of a 10-week computer-assisted cognitive remediation (CACR) program (see Meusel et al., submitted for a complete description of the behavioural results). Patients were eligible to participate if they: i) had a *Structured Interview for DSM-IV, Axis I Disorders, Patient version*[18] (SCID-I/P) confirmed diagnosis of BD or MDD; ii) were euthymic or had stable subsyndromal symptoms at baseline; iii) were between the ages of 18 and 60 years; and iv) were able to provide written informed consent. Exclusion criteria included: i) treatment with anti-cholinergic or typical (first generation) anti-psychotic medication; ii) electroconvulsive

therapy (ECT) or transcranial magnetic stimulation (TMS) within the past year; iii) a history of substance dependence or significant and recent (< 1 year) substance abuse; iv) a history (within the past 12 months) of an endocrine or other medical disorder known to adversely affect cognition (e.g., Cushing's, uncontrolled diabetes, seizure disorder); and v) English comprehension lower than a grade 6 reading level. The protocol was approved by the research ethics board at St. Joseph's Healthcare. Patients who participated in the fMRI portion of the study reported here were scanned at baseline (PRE), and immediately following completion of the remediation program (POST). We also recruited thirty-eight healthy control (HC) subjects, to compare functional activation and task performance in the patient sample at baseline with that of a normative sample. HC subjects had no psychiatric history, as assessed with the SCID-I/P.[18] After a complete description of the study procedures, written informed consent was obtained from each subject.

Computer –Assisted Cognitive Remediation (CACR)

Cognitive training consisted of 20 computer tasks from PSSCogRehab,[19] a restitution-based computer-assisted cognitive remediation (CACR) program for improvement of selective attention, working memory, executive function, sensorimotor skills, declarative memory, and problem solving. Training using this program is hierarchically organized, with successful completion of all the tasks in

one module required before beginning a new module. Patients trained in individual one-hour sessions, three hours a week, for ten weeks.

Neuropsychological tests

Recollection memory was assessed using the Hopkin's Verbal Learning Test-Revised[20] (HVLT), and working memory was assessed using the WAIS-R Digit Span Backward subtest.[21] These tests were administered to the patients as part of a larger neuropsychological test battery before and immediately following the last session of remediation.

Imaging tasks

Working memory: n-back task. An abstract object recognition n-back task (Figure 1) was presented over four scan runs (A, B, C, and D). A 0-back, 1-back, and 2-back block were each presented twice within a run. Each block contained a total of 14 presented images, however only 12 of these trials were used for analysis. Because participants were not required to respond until the third trial during the 2-back condition, we discarded the first two trials of every block, regardless of condition, to maintain consistency. Therefore, one scan run consisted of 24 trials of each memory condition. The 0-back and 1-back condition included 19 non-target and 5 target trials and the 2-back condition included 18 non-target and 6 target trials.

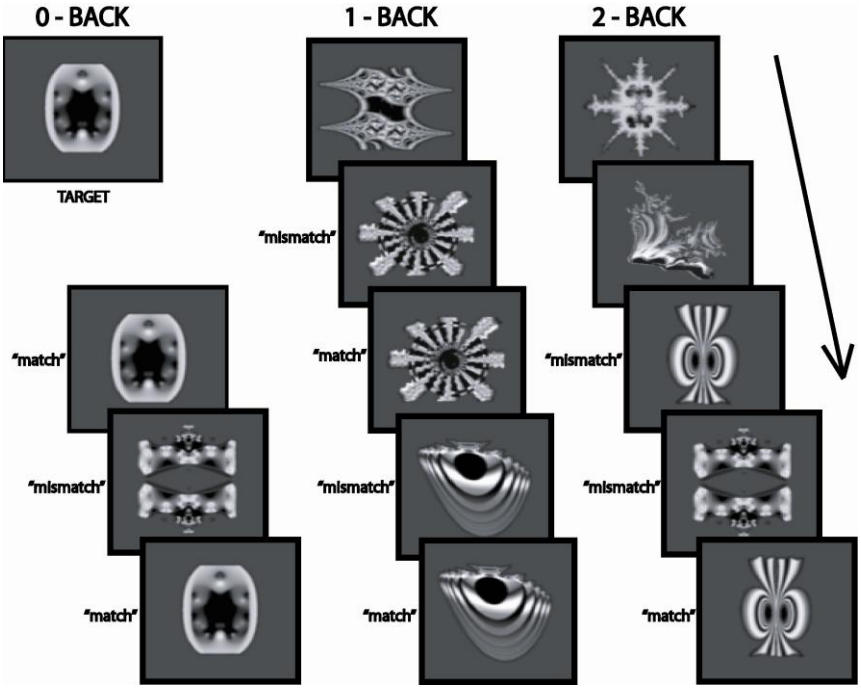

Figure 1: A visual depiction of the n-back task. Participants pressed a button with their middle finger on "match" trials, and pressed a second button with their index finger on "mismatch" trials.

For the 1-back, participants were asked to press a button with their middle finger when the current image matched the image presented on the immediately preceding trial, or to press a second button with their index finger for those trials when the current image *did not* match the image presented on the immediately preceding trial. Similarly, during the 2-back, participants were asked to press a button with their middle finger when the current image matched the image presented two trials back, or to press a second button with their index finger when the current image *did not* match the image presented two trials back. For the 0-back control condition, participants pressed the middle-finger button whenever a

pre-specified "target" image appeared (the image was specified on the instruction screen presented at the beginning of each block). For all other images, participants pressed the index-finger button. Responses were collected using a MR compatible Current Designs (Current Designs, Inc., Philadelphia, PA) button box strapped to the participant's dominant hand.

E-Prime (www.pstnet.com) was used to present the task and collect responses. Stimuli were projected down the bore of a magnet onto the screen of a visor viewed through a mirror resting on the head coil. On each trial, a uniform-sized image was presented for 500 ms, followed by an inter-stimulus interval of 2000 ms. A blank screen was presented for 30 seconds between each block. An instruction screen was presented for 7500 ms at the beginning of each block to orient the participant to the new condition (i.e., 0-back, 1-back, or 2-back). During a block, no feedback was given regarding correct or incorrect responses. Each run had a total scan time of 7 minutes 15 seconds. A brief rest period separated one scan run from the next. The order of scan runs (i.e., A, B, C, and D) was randomized across participants, and across visits (i.e., PRE versus POST).

Recollection memory-process dissociation task. Participants completed a recollection memory task adapted for scanning[15] from a behavioural protocol that has previously shown differences in recollection memory, but not habit memory, in patients with mood disorders compared to control subjects.[22, 23] In the first phase of this task, participants were trained outside of the scanner with a series of

18 word pairs. Each pair consisted of a single word prime (e.g., *bridge*) matched with two possible associates (e.g., *river* or *water*). Word pairs were presented on a computer screen as a word + word fragment combination (e.g., *bridge* - _ _ _ e r). Participants were given 2 seconds to fill in the word fragment verbally before the computer presented an answer. This phase of the task was used to create habit associations for certain word pairings, as the computer presented one word pair (e.g., *bridge-river*) at a higher frequency (67% of trials) than the other potential word pair (e.g., *bridge-water*; 33% of trials).

Inside the scanner, participants were presented with word lists to study made up of habit and recollection word pairings from the training phase. Each study list contained 6 habit pairs (high frequency match) and 3 recollection pairs (low frequency match). The complete word pairs appeared on the screen for 1000 ms, followed by a 500 ms fixation cross. Participants were instructed to read the word pairs aloud and remember them for a subsequent memory test. Immediately following the study list, participants carried out a brief mathematical distractor task to eliminate primacy and recency effects. Following this, the memory test was presented. Here, participants were shown 11 word + word fragment combinations (i.e., *bridge* - _ _ _ e r), comprised of the six habit word pairs and the three recollection word pairs from the immediately preceding study list. In addition, two word pairs that were not included in the study list were presented to assess each participant's tendency to guess. Participants were instructed to

respond verbally by completing the word fragments with the words from the immediately preceding study list, or to provide their best guess if they could not remember. Recollection scores were obtained by subtracting recollection trial probability (i.e., the probability of responding with a habit association on trials where the study list word-pairs were the same as the low frequency word-pairs during training) from habit trial probability (i.e., the probability of responding with a habit association on trials where the study list word-pairs were the same as the high-frequency word-pairs during training.

The task was divided into five scan runs; the first two runs had four study-test lists, and the last three runs had three study-test lists. There were two versions of the training according to which word pairing was presented at higher frequency; the two versions were distributed equally across participants at the baseline visit. At the POST visit, patients completed the version of the task that was *not* completed at the baseline visit.

Image acquisition

The imaging session for each task lasted approximately one hour. Patients were given the option of completing both tasks on the same day, or on different days to minimize fatigue. All imaging was performed using a 3-Tesla General Electric scanner equipped with an 8-channel parallel receiver birdcage head coil (General Electric, Milwaukee, WI.). For the n-back task, 34 axial slices (3 mm thick, no skip) across the whole brain were imaged using an echo planar pulse

sequence [echo time (TE) = 35 ms; repetition time (TR) = 2500 ms; acquisition matrix = 128 × 64; FOV=24cm; flip angle = 90°]. A high-resolution full brain T1-weighted anatomical scan in the axial orientation was obtained prior to functional imaging. The scanning parameters for the anatomical image series were: 3D SPGR pulse; fast IRP sequence; prep time = 450; flip angle= 12; FOV = 240; TE = 2.1; TR system set = 9; slice thickness = 2 mm; frequency matrix = 320; phase matrix = 192; frequency direction = A/P).

For the recollection memory task, 13 axial slices (3 mm thickness) centered on the hippocampus were imaged using an echo planar pulse sequence [echo time (TE) = 43 ms; repetition time (TR) = 3000 ms; acquisition matrix = 128 × 64; FOV = 40x20; flip angle = 90°]. A 3-second gap was built into the scanner sequence after each TR in order to produce a silent period during which the subject was asked to respond verbally. A high resolution T1-weighted anatomical scan in the sagittal orientation was obtained prior to functional imaging. The scanning parameters for the anatomical image series were: 3D SPGR pulse; fast IRP sequence; prep time = 300; flip angle = 20; FOV = 240; TE = 2.1; TR system set = 9; slice thickness = 1.2 mm; frequency matrix = 256, phase matrix = 256.

fMRI processing and statistical analyses

Acquired images were preprocessed and analyzed using Brain Voyager QX version 2.3.0 (Brain Innovation B.V., Maastricht, Netherlands). The

functional data sets were slice-time corrected, 3D motion corrected and realigned to the third volume in the first series collected, high-pass filtered at 3 cycles/time course, and normalized to Talairach space.[24] The high-resolution T1-weighted three-dimensional anatomical MR data sets were transformed into Talairach space, used for co-registration with each participant's functional data sets, and then averaged across participants to generate a composite image onto which the functional activation results were projected.

To examine neural responses to the memory tasks at baseline in the patient sample, we constructed two within-subject general linear models (GLMs); memory load (0-back, 1-back, or 2-back) was set as the within-subject factor for one, trial type (recollection, encoding) was the within-subject factor for the second. GLMs with the same structure were used to examine neural responses to the memory tasks in the healthy control sample.

To contrast activation in the patient sample at baseline with that of the HC sample directly, we constructed two GLMs with memory load (0-back, 1-back, or 2-back) or trial type (recollection, encoding) as within-subject factors, and group (HC vs. patients) as a between-subjects factor.

To examine neural activation before and after cognitive remediation, we constructed two more within-subject GLMs. Visit (PRE, POST), and memory load (0-back, 1-back, or 2-back) or trial type (recollection, encoding) were within-subject factors. All contrasts were corrected for multiple-comparisons using a

cluster-level statistical threshold estimator; the average statistical values for the resulting regions of interest are reported.

Results

Excluding scans that were discarded because of excessive movement (> 2 mm or technical error; *n* = 21), 15 HCs [mean age = 39.7 (sd = 14.3); mean education (years) = 17.0 (sd = 3.7); 5 M, 10 F] and 35 patients completed the n-back task at baseline, and 18 HCs [mean age = 40.3 (sd = 11.0); mean education (years) = 17.3 (sd = 3.2); 11 M, 7 F] and 38 patients completed the recollection memory task at baseline. Twenty-three patients had complete PRE-POST n-back imaging data, and 28 patients had complete PRE-POST recollection task imaging data. Demographic comparisons showed no significant differences in age or education between HCs and patients at baseline. There was, however, a significant difference in sex ratio between the HC and patient groups (*p's* < .01); there were a greater proportion of women in the n-back patient group at baseline (7 M, 28 F) and in the recollection task patient group at baseline (8 M, 30 F). Demographic and clinical information for the PRE-POST patient sample is listed in Table 1.

Table 1: Demographic and clinical information for the PRE-POST sample

	n-back	*Recollection*
	n = 23	*n* = 28
	mean (SD)	mean (SD)
Age	49.7 (7.7)	49.4 (8.0)
Sex ratio	6 M; 17 F	5 M; 23 F
Education (years)	15.8 (3.5)	15.6 (3.5)
NART-estVIQ	109.7 (9.0)	108.9 (8.7)
Diagnosis	5 BD; 18 MDD	9 BD; 19 MDD
17-item HRSD (PRE)	9.4 (5.6)	8.6 (5.6)
17-item HRSD (POST)	9.9 (5.3)	8.5 (5.3)
Illness duration (years)	24.4 (12.7)	26.0 (12.2)
Medication load	3.0 (2.1)	3.0 (2.0)

NART-estVIQ[49, 50] = National Adult Reading Test estimated verbal IQ; HRSD[51] = Hamilton Rating Scale for Depression

Task performance

Behavioural scores on the n-back and recollection memory tasks are presented in Table 2. We compared memory scores from the patient samples at baseline with those of the HCs. On the 0-back and 1-back condition, the patients and HCs had comparable accuracy scores; however, reaction times were significantly slower for patients. In the 2-back condition the speed-accuracy trade-off shifted; the difference in reaction times between groups was no longer significant, however accuracy scores were significantly lower in the patient group.

Table 2: Task performance in the healthy control (HC) and patient groups at baseline, and in the patient sample before (PRE) and following (POST) remediation

n-back task	*HCs* *n = 15* mean (SD)	*Patients* *n = 35* mean (SD)	*p*	*PRE* *n = 23* mean (SD)	*POST* *n = 23* mean (SD)	*p*
Accuracy						
0-back	.73 (.04)	.72 (.07)	.50	0.72 (.08)	0.72 (.10)	.97
1-back	.83 (.20)	.86 (.06)	.37	0.87 (.05)	0.87 (.07)	.82
2-back	.81 (.05)	.76 (.06)	.04*	0.78 (.06)	0.77 (.08)	.82
Reaction time						
0-back	448.9 (75.7)	544.5 (86.4)	<.01*	557.8 (83.1)	557.0 (118.9)	.98
1-back	569.6 (133.9)	710.0 (141.8)	<.01*	714.3 (141.0)	706.9 (169.8)	.87
2-back	684.9 (232.6)	816.8 (184.4)	.06	835.1 (195.4)	818.9 (229.2)	.80

Recollection memory task	*HCs* *n = 18* mean (SD)	*Patients* *n = 38* mean (SD)	*p*	*PRE* *n = 28* mean (SD)	*POST* *n = 28* mean (SD)	*p*
Recollection	.52 (.13)	.32 (.20)	<.01*	.34 (.16)	.38 (.18)	.51
Habit	.61 (.10)	.56 (.09)	.06	.57 (.09)	.55 (.10)	.55
Guessing	.63 (.11)	.59 (.12)	.20	.61 (.10)	.55 (.13)	.07

On the recollection task, recollection memory scores were significantly lower in patients. There was no difference in habit memory or propensity to guess between the two groups.

In the PRE-POST patient sample there were no significant changes in accuracy or reaction time following remediation, nor were there any significant changes in recollection memory, habit memory, or propensity to guess.

Baseline imaging

n-back task. We contrasted activation on the 1-back and 2-back condition against the 0-back control condition, in patients with baseline n-back scans (n = 35). Under low memory demand (1-back), there were significant activation increases in: bilateral middle frontal gyrus (BA 9/6); right medial frontal gyrus (BA 8); bilateral insula (BA 13); right middle temporal gyrus (BA 21); left superior temporal gyrus (BA 22); left fusiform gyrus (BA 37); and right supramarginal gyrus and left inferior parietal lobule (BA 40). Under high memory demand (2-back), we observed a similar pattern of activation increases in: bilateral precentral gyrus (BA 9); right medial frontal gyrus (BA 8); right middle frontal gyrus (BA 10); right middle temporal gyrus (BA 21); left superior temporal gyrus (BA 22); left fusiform gyrus (BA 20); left parahippocampal complex (BA 19/30); and right supramarginal gyrus (BA 40). Detailed results are presented in Table 3, and illustrated in Figure 2.

We also contrasted activation in the HCs on the 1-back and 2-back condition against the 0-back control condition. Under low memory demand (1-back), healthy controls had significant activation increases in: bilateral insula (BA 13); and right superior parietal lobule and precuneus, bilaterally (BA 7). Under high memory load, activation increased in: bilateral middle frontal gyrus and left precentral gyrus (BAs 6/9); right insula (BA 13); left medial frontal gyrus (BA

32); and left precuneus (BA 19). Detailed results are presented in Table 4 and illustrated in Figure 2.

Table 3: Memory contrasts in the patient sample at baseline

	x	y	z		Region	Brodmann Area	t	# voxels	*p*
1-back > 0-back	35	25	33	R	middle frontal	9	4.54	3511	.00001
	-52	28	36	L	middle frontal	9	5.15	9285	.000001
	-25	-5	48	L	middle frontal	6	3.63	173	.0004
	5	22	45	R	medial frontal	8	3.65	203	.0003
	32	19	9	R	Insula	13	3.52	164	.0005
	-31	16	9	L	Insula	13	3.60	121	.0004
	62	-38	-9	R	middle temporal	21	3.58	226	.0004
	-55	-26	0	L	superior temporal	22	3.65	126	.0003
	-42	-47	-9	L	Fusiform	37	5.25	6647	0
	41	-47	36	R	supramarginal	40	4.43	6628	.00002
	-43	-53	42	L	inferior parietal	40	5.04	9535	.000001
0-back > 1-back	2	55	21	R	medial frontal	10	-4.38	2508	.00002
	47	10	-15	R	superior temporal	38	-3.52	78	.0005
2-back > 0-back	35	43	24	R	middle frontal	10	4.52	1150	.00001
	5	22	45	R	medial frontal	8	5.41	7946	0
	38	22	36	R	precentral	9	6.15	20836	0
	-40	7	36	L	precentral	9	7.03	31825	0
	65	-38	-9	R	middle temporal	21	4.24	5356	.00003
	-55	-26	0	L	superior temporal	22	3.58	379	.0004
	-55	-35	-21	L	Fusiform	20	4.41	6635	.00002
	-28	-50	6	L	parahippocampal	30	3.45	228	.0007
	-35	-41	0		parahippocampal	19	3.53	275	.0005
	44	-47	36	R	supramarginal	40	6.53	67281	0
0-back > 2-back	-13	40	43	L	superior frontal	8	-3.72	230	.003
	17	31	-2	R	medial frontal	10	-3.27	232	.001
	2	43	0	R	anterior cingulate	32	-4.67	11225	0
	56	-8	-15	R	inferior temporal	21	-3.23	57	.001
	32	-5	-21	R	amygdala		-3.26	272	.001
	23	-29	-15	R	parahippocampal	35	-3.42	255	.0008
	-40	4	-15	L	superior temporal	38	-4.59	1091	0
	-52	4	-24	L	middle temporal	21	-3.21	59	.002
	-40	-17	-24	L	Fusiform	20	-3.57	54	.0004
	-1	-56	21	L	posterior cingulate	23	-3.33	496	.001
Recollect > Study	38	-8	-21	R	Fusiform	20	2.56	184	.01
	-25	-17	-12	L	hippocampus		3.01	359	.003
	-39	-14	-18	L	inferior temporal	20	2.86	220	.005
	20	-41	1	R	Lingual	30	4.05	337	.00007

Table 4: Memory contrasts in the healthy control sample

	x	y	z		Region	Brodmann Area	t	# voxels	*p*
1-back > 0-back	35	19	9	R	Insula	13	3.49	79	.0006
	-34	11	21	L	Insula	13	4.22	2399	.00004
	-34	19	3	L	Insula	13	3.64	189	.0004
	26	-74	48	R	superior parietal	7	3.43	127	.0007
	26	-68	33	R	Precuneus	7	3.68	209	.0003
	-28	-65	36	L	Precuneus	7	3.81	1212	.0002
0-back > 1-back	-1	55	21	L	medial frontal	10	-3.60	293	.0004
2-back > 0-back	32	19	6	R	Insula	13	5.41	3723	0
	38	16	33	R	middle frontal	9	5.33	11286	0
	29	-2	48	R	middle frontal	6	5.20	5457	.000001
	-43	19	33	L	middle frontal	9	5.27	23087	0
	-7	13	45	L	medial frontal	32	5.75	8158	0
	-31	-8	48	L	Precentral	6	3.71	522	.0003
	-31	-65	36	L	Precuneus	19	5.35	42821	0
0-back > 2-back	2	43	6	R	anterior cingulate	32	-3.77	415	.0002
	-7	55	15	L	medial frontal	10	-3.77	368	.0002
	50	7	-30	R	middle temporal	21	-3.51	65	.0006
	38	-2	-30	R	middle temporal	21	-3.71	653	.0003
	38	13	-24	R	superior temporal	38	-3.64	267	.0003
Recollect > Study	-10	-2	-15	L	parahippocampal	34	3.61	838	.0004
Study > Recollect	32	-20	-22	R	parahippocampal	36	-3.34	158	.001
	20	-17	-9	R	parahippocampal	35	-4.25	155	.00003
	-16	-35	-3	L	parahippocampal	30	-4.13	1344	.00005
	-36	-31	-12	L	parahippocampal	36	-3.41	96	.0008

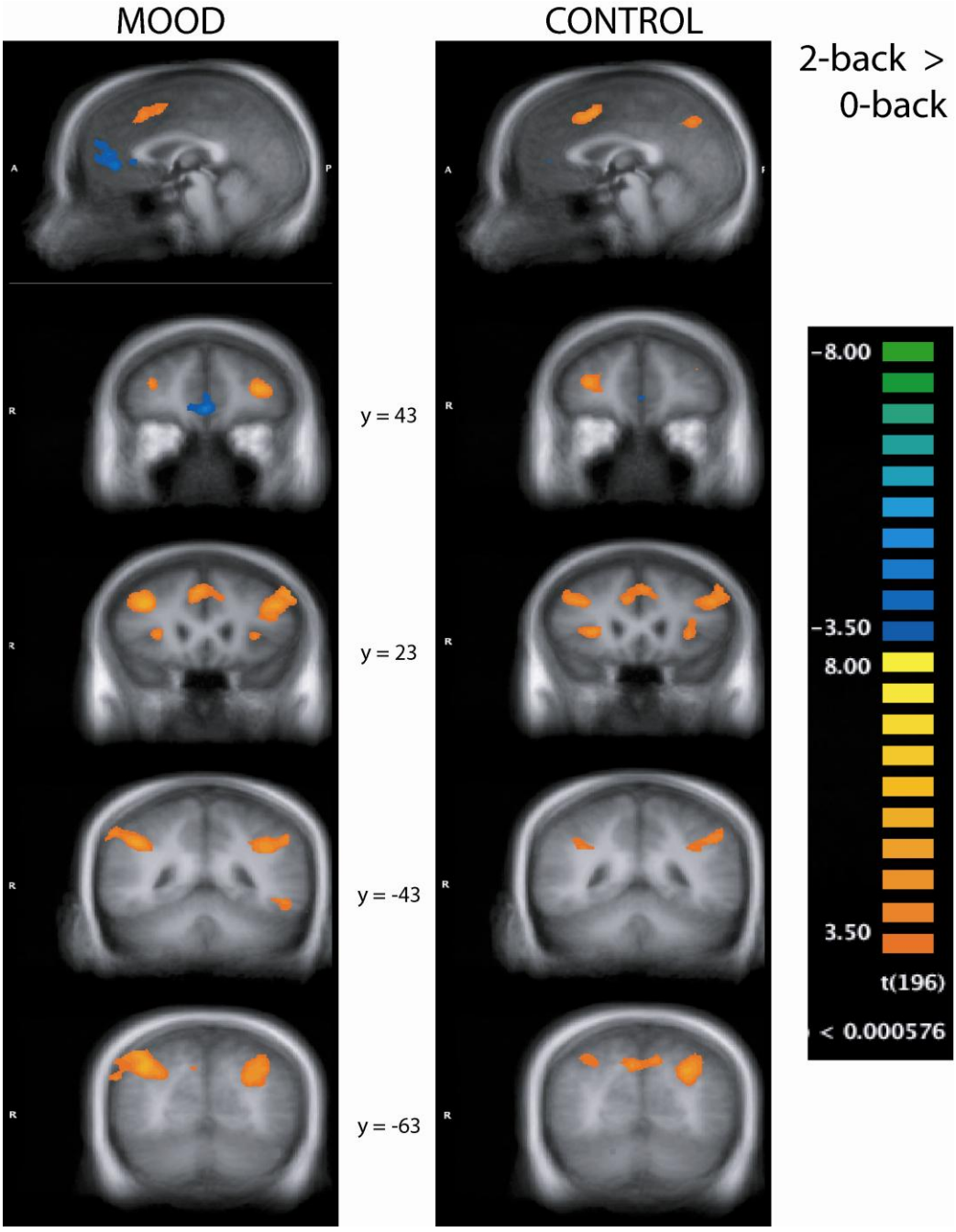

Figure 2: Within-group contrasts (2-back vs. 0-back) for the patient sample at baseline (n = 35), and for the healthy control sample (n = 15).

Under low memory demand, both patients and HCs showed down regulation in the medial frontal gyrus (BA 10). Patients also showed deactivation in the right superior temporal gyrus (BA 38). Under high memory demand, a more extensive pattern of deactivation was observed in patients; again, within the right medial frontal gyrus (BA 10), but also in: right anterior cingulate (BA 32); left superior frontal gyrus (BA 8); right inferior temporal gyrus (BA 21); right parahippocampal complex (BA 35); left superior and middle temporal gyri (BAs 38/21); left fusiform gyrus (BA 20); left posterior cingulate (BA 23), and right amygdala. Healthy controls showed deactivation at high memory demand in: right anterior cingulate (BA 32); left medial frontal gyrus (BA 10); and in right middle and superior temporal gyri (BAs 21/38) (Tables 3 and 4).

A direct comparison of HCs and patients showed that HCs had significantly greater activation than patients in the 2-back condition in the superior frontal gyrus (BA 10). There were no significant between-group differences in activation in the 1-back condition (Table 5).

Recollection memory task: We contrasted activation on recollection trials against the study-list encoding period, in patients with baseline recollection task scans (n = 38). On recollection trials, activation was increased significantly in the left hippocampus. We also contrasted activation in the HCs on recollection trials

Table 5: Healthy controls versus patients at baseline

	x	y	z		Region	Brodmann Area	t	# voxels	*p*
2-back									
HC > Patients	32	64	15	R	superior frontal	10	3.75	231	.0002
Recollection									
HC >	9	-8	-21	R	parahippocampal	34	6.12	2107	0
Patients	-10	-7	-21	L	parahippocampal	34	3.22	207	.001
	20	-17	-9	R	parahippocampal	35	-4.81	335	.000003
	-19	-35	0	L	parahippocampal	27	-4.46	1531	.00001
Patients >	-36	-31	-12	L	parahippocampal	36	-3.17	127	.002
HC	38	-8	-23	R	Fusiform	20	-3.24	88	.001
	-40	-11	-24	L	Fusiform	20	-2.61	58	.01
	20	-40	-3	R	Lingual	30	-4.59	1075	.00001

against the study-list encoding period. HCs showed increased activation in left parahippocampal complex (BA 34), but *deactivation* in more posterior regions of parahippocampal complex, bilaterally (BAs 30, 35, 36). Detailed results are presented in Tables 3 and 4 and illustrated in Figure 3.

A direct comparison of HCs and patients found that HCs had significantly greater activation on recollection trials in the anterior parahippocampus complex, bilaterally (BA 34), whereas patients showed greater activation in a more posterior region of parahippocampal complex, bilaterally (BAs 27, 35, 36). Detailed results are presented in Table 5.

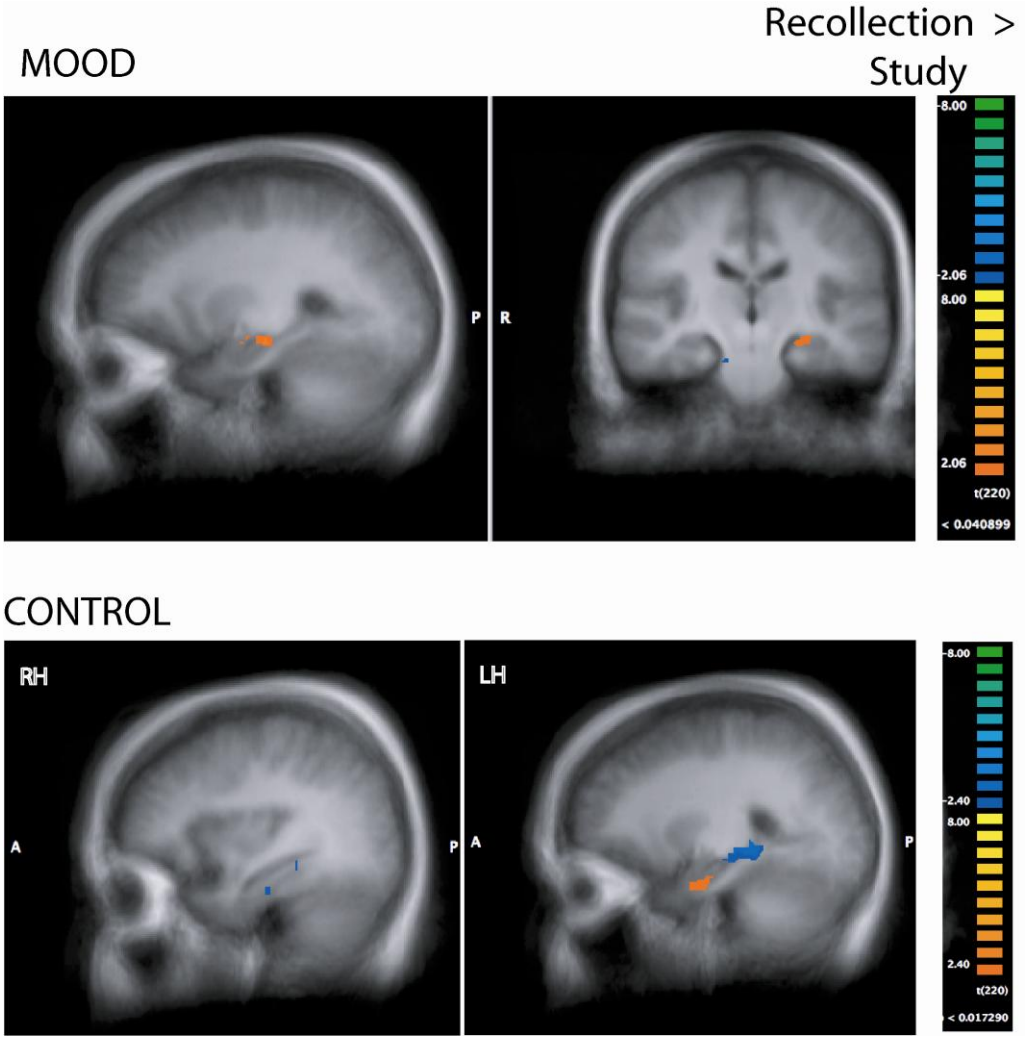

Figure 3: Within-group contrasts (recollection trials vs. study-list encoding) for the patient sample at baseline (n = 38), and for the healthy control sample (n = 18).

PRE-POST training comparisons

A contrast of memory load (1-back versus 0-back) and visit (PRE versus POST) found no significant activation differences following training in the 1-back condition. A similar contrast (2-back versus 0-back) revealed significantly greater

activation at POST, compared to PRE, in dorsolateral and ventrolateral frontal cortices [superior frontal gyri, bilaterally (BA 6/8)], medial frontal cortices, bilaterally [left medial frontal gyrus (BA 8); right cingulate gyrus (BA 32)], and in the right superior temporal gyrus (BA 38).

On the recollection memory task, contrasts of trial type (recollection versus study-list encoding) and visit (PRE versus POST) found significantly greater activation on recollection memory-dependent trials at POST, compared to PRE, in the right hippocampus. Detailed results are presented in Table 6 and illustrated in Figures 4 and 5.

Neuropsychological test performance. Patients showed a significant improvement following remediation on the backward digit span, a test of working memory, F (1, 38) = 4.62, p = .04 (PRE: mean = 6.4, sd = 2.5; POST: mean = 8.1, sd = 2.5). There was no significant change in performance on the delayed recall portion of the HVLT (PRE: mean = 42.1, sd = 15.0; POST: mean = 43.3, sd = 13.7).

Table 6: PRE-POST comparison

	x	y	z		Region	Brodmann Area	t	# voxels	*p*
2-back	8	37	45	R	superior frontal	8	3.32	55	.001
	-22	13	49	L	superior frontal	6	3.15	69	.002
POST >	11	31	30	R	cingulate	32	3.14	52	.002
PRE	-10	19	48	L	medial frontal	8	3.10	69	.002
	44	16	-18	R	superior temporal	38	3.18	66	.002
Recollection									
POST > PRE	26	-20	-15	R	hippocampus		3.94	73	.0001

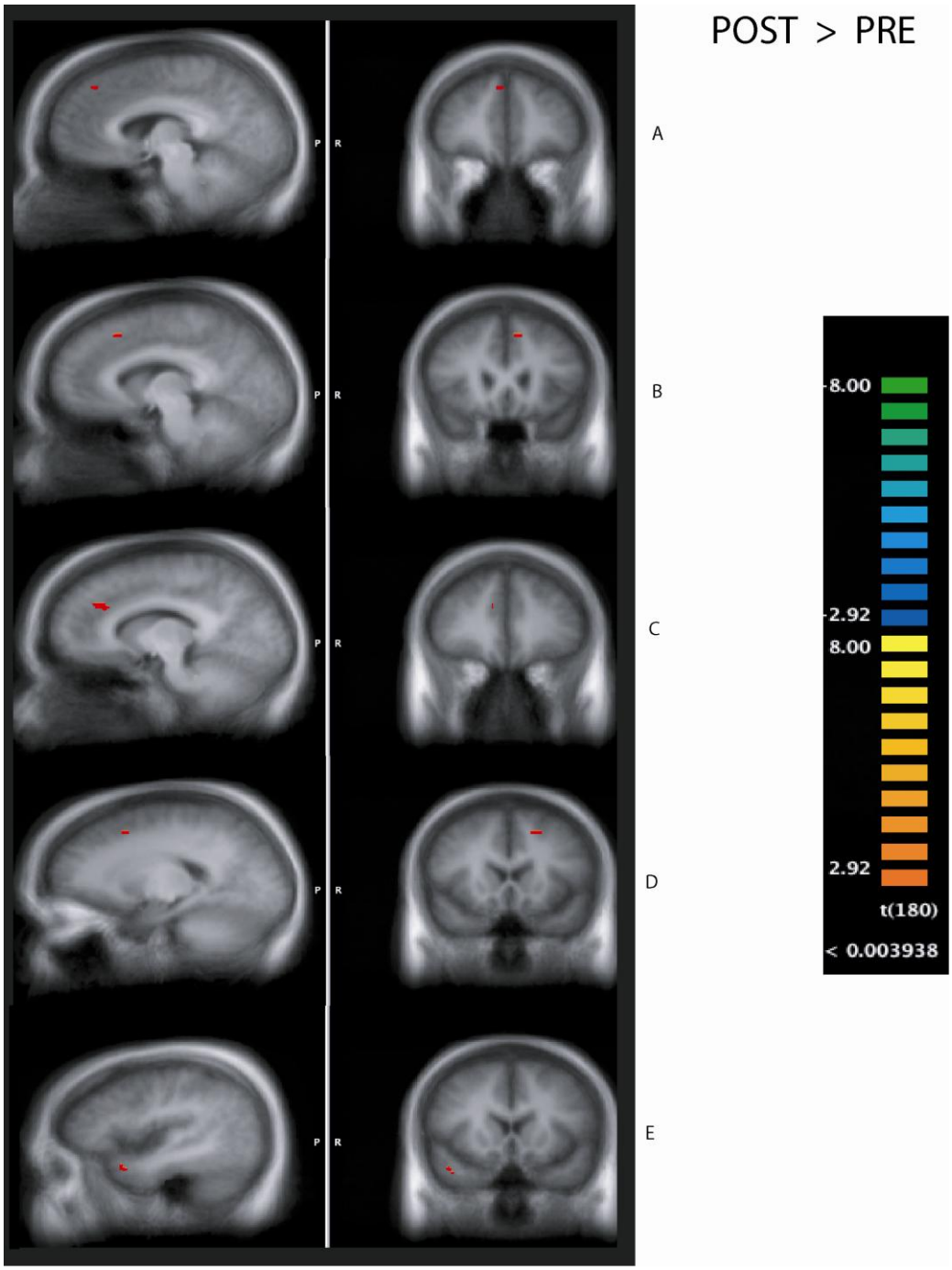

Figure 4: PRE-POST n-back comparison in the patient sample (*n* = 23). Activation increased following remediation in the right and left superior frontal gyrus (A and B), in the right cingulate (C), in the left medial frontal gyrus (D), and in the right superior temporal gyrus (E).

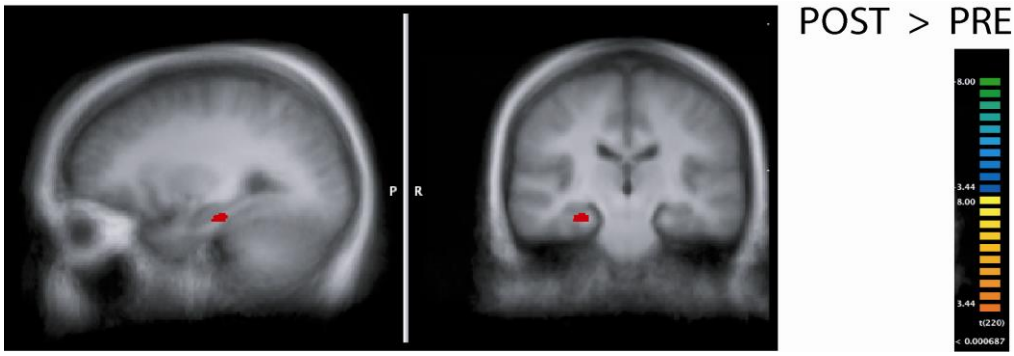

Figure 5: PRE-POST recollection task comparison in the patient sample (*n* = 28). Activation increased following remediation in the right hippocampus.

Comment

Cognitive remediation is emerging as an effective treatment for individuals who experience cognitive problems related to a mood disorder. There is relatively strong evidence for improvement in domains of working memory and verbal memory following remediation.[2, 25, 26] We have an extremely limited understanding of the changes in brain activity that are associated with these interventions, however. We therefore examined neural activation in patients prior to and following remediation.

Baseline imaging

In control subjects and in baseline patient scans, we observed the predicted pattern of *increased* activation with increasing memory load in frontoparietal control networks, and *decreased* activation with increasing memory load in medial regions of the frontal, parietal, and anterior temporal lobe. The only

significant difference between patients and controls when compared directly was in an area of frontopolar cortex, where patients had less activation at high memory load. This finding is consistent with reports of structural and functional alterations in frontopolar cortex in patients with BD[27] and MDD,[28] and may contribute to the difficulty that patients have in behavioural performance during conditions of high memory load. Indeed, significant differences in activation between patients and healthy controls in frontopolar cortex were reduced to the level of a trend when performance on the 2-back task was controlled,[29] further evidence of this region's role in supporting task demand. These findings are also consistent with theoretical accounts of frontopolar function that implicate this area in the integration of multiple cognitive operations,[30] and in the coordination of motivational, emotional, and executive capacities.[31]

Although direct contrasts only showed significant differences in activation between patients and healthy controls in frontopolar cortex, within-group comparisons found that patients had significantly increased activation in the temporal lobe with increasing memory demand. Conversely, healthy control subjects did not engage any regions within the temporal lobe to a significant extent; only frontal and parietal regions were recruited to support performance. Temporal lobe structures are not typically associated with working memory performance in normative samples,[32] however activation within medial and lateral temporal regions has been reported in other studies of patients with MDD or BD

during n-back task performance.[11, 14, 33] Temporal activation with increasing memory load has also been observed in young adults at increased familial risk for depression.[34] Whether increased temporal activation is a compensatory mechanism in patients with mood disorders that supports working memory performance requires further clarification.

On the recollection memory task, healthy control subjects engaged anterior medial temporal regions during recollection, whereas patients engaged more posterior medial and lateral temporal regions. Direct comparison confirmed these differences between groups to be significant. This is consistent with our recent report of increased activation in anterior medial temporal regions in healthy controls, relative to patients with MDD, using the same fMRI task in another patient sample.[15] Moreover, anterior regions of the medial temporal lobe, including CA1 and the subiculum, have been previously linked to episodic memory retrieval.[35, 36] Thus, poorer recollection memory performance in the patient group is likely a result of decreased engagement of this region. Further research is needed to determine whether increased activation in the patient sample in the *posterior* parahippocampal complex during recollection, a region more closely linked to episodic encoding in normative populations,[35, 37, 38] reflects a compensatory or adaptive response to encoding and retrieval demands.

PRE-POST training comparison

Following remediation, we observed increased activation on the n-back task in regions of lateral and medial prefrontal cortex, and in the dorsal cingulate. Increased activation in these regions may reflect changes in the neural circuitry that supports working memory function specifically.[32] Alternatively, these activation increases could reflect functional alterations within more domain-general networks involved in sustained attention and cognitive control,[39-42] given that the n-back task was quite dissimilar to the tasks used during training. A recent imaging study of cognitive remediation in patients with multiple sclerosis showed increased activation in dorsal frontal, posterior cingulate, and parietal cortices on a trained alertness task following remediation, but also on a more complex, untrained attention task.[43] The authors suggest that cognitive training stimulated domain-general attentional networks mediated by frontal, cingulate, and parietal regions, and that improved performance on the untrained task was due to enhanced focus and attentional control.[43] This explanation is consistent with our own findings, and also with behavioural evidence that suggests CACR exerts a "non-specific" beneficial effect on attention and executive function.[25]

We also observed activation increases within the right hippocampus during recollection memory task performance following training. Critically, this region is almost identical to the region in the right hippocampus where we

previously reported greater activation in healthy controls relative to patients with MDD during recollection memory.[15]

Links between behavioral improvement and functional activation

Patients had significant improvement on a neuropsychological test of working memory following remediation, providing some evidence for behavioural change corresponding to the observed patterns of change in activation. Delayed recall performance did not change however, despite evidence of increased hippocampal activation. It is possible the greatest performance benefits following CACR occur on tasks that are similar to the training tasks; indeed, some of the training tasks[19] closely resembled the digit span task—where we did find improved performance following remediation—whereas the delayed recall task incorporated a substantially longer delay relative to the tasks used during training (20 minutes versus 3 minutes), and the n-back paradigm and the recollection memory-process dissociation task used during scanning were substantially different than any of the training tasks. Thus, the observed activation increases during the n-back task and the recollection memory task, in the absence of overt improvements to performance, may reflect remediation-induced neural reorganization or strengthening within domain-general frontal and temporal control networks implicated in various monitoring and executive processes that coordinate and adjust ongoing goal-directed behaviors.[44, 45, 46] Further work is needed to determine whether behavioural improvements on untrained or more

complex tasks require a longer course of training, or an adjunct form of remediation (i.e., strategy-based) to promote generalization.

Limitations and further investigations

The present study has several limitations. Notably, our patient group included individuals with BD or MDD, and there may be differences between these groups. Exploratory analyses showed the same pattern of findings across both patient groups, however, and this is consistent with literature that suggests that the major differences in the pattern of cognitive dysfunction between the groups are not qualitative, but rather quantitative, reflecting a greater severity of cognitive dysfunction in patients with BD. Another limitation of the present study is the fact that our healthy comparison groups were scanned only once; thus, we were not able to control for any functional activation changes in the patient sample that may have resulted from repeat testing. Finally, although psychotropic medication has been shown to have little effect on functional neuroimaging measures in patients with BD, [52] it is possible that some of the observed differences in activation between patients and healthy controls were influenced by medication status. Variability in medication load across patients should not have influenced our PRE-POST remediation contrasts, however, as this was a within-subject comparison, and medications were stable over training.

Conclusions

The findings reported here demonstrate the potential for neuroplastic changes in the lateral and medial prefrontal regions that support working memory,[32] and in medial temporal regions that subserve recollection memory.[15] Moreover, these findings are consistent with reports of improved working memory and delayed recall in a larger sample of patients with mood disorders following cognitive remediation.[47] Taken together, these results provide some of the first evidence for functional change following cognitive remediation in patients with mood disorders.

Imaging core cognitive processes before and after a course of cognitive remediation can provide important information about how these treatments exert their effects, and how to maximize efficacy. Indeed, the translation of neuroplasticity research to clinical therapies has been highlighted as an important avenue for further study.[48]

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CHAPTER 5

AFTERWORD

The analyses presented in Chapters 2, 3, and 4 provide convergent behavioural and functional imaging evidence to support the utility of cognitive remediation for individuals with BD and MDD. Although further research is needed to clarify the specificity and stability of these effects, our findings contribute to a growing body of literature that shows computer-assisted cognitive remediation to be an effective cognitive management strategy across a range of psychiatric and neurological disorders.

In Chapter 2, we measured neuropsychological functioning in stable, subsyndromal patients with BD or MDD, to determine whether quantifiable differences in cognitive functioning exist between these two diagnostic groups. We found that during subsyndromal periods, patients with BD and patients with MDD experience a similar degree of deficit on tasks of processing speed, working memory, and mental flexibility, whereas patients with BD experience a greater degree of deficit on tests of delayed recall and verbal fluency. Patients with MDD performed better on these tasks than patients with BD, but not as well as healthy controls; their performance was not significantly different from either comparison group. Thus, in patients with MDD, deficits within these domains may be particularly subtle, or restricted to particular subgroups, such as those with extensive illness burden (e.g., MacQueen et al., 2002). In patients with BD, the finding of *greater* relative deficit on tests of verbal memory and verbal fluency is

consistent with the possibility that these deficits comprise a cognitive endophenotype (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009). Clinically, these findings converge on processing speed, working memory, and executive functioning as targets for intervention in BD and MDD, and on verbal memory and verbal fluency as cognitive domains that may be particularly important to address in patients with BD.

In Chapter 3, we investigated the efficacy of a 10-week computer-assisted cognitive remediation intervention for patients with BD and MDD. Following remediation, patients improved significantly on neuropsychological tests of verbal delayed recall and working memory. Subjective assessment of cognitive and psychosocial functioning also improved post-remediation—evidence for generalization of gains. We identified two factors that impacted response to treatment as well: depressive symptom severity and motivation. Together, these findings represent the first comprehensive investigation of cognitive remediation therapy for patients with mood disorders, and provide a platform for future research within this area of study.

In Chapter 4 we explored the neural correlates of working memory and recollection memory in patients with mood disorders. We compared functional activation in patients prior to remediation with functional activation in a healthy control sample. Then we contrasted pre- and post-training activation in a subsample of patients who completed functional scans before *and* after the

intervention. Prior to remediation, during the n-back working memory task, patients showed the predicted pattern of *increased* activation at high memory load in frontoparietal control networks. Patients also activated medial and lateral temporal regions with increasing memory load, a pattern that was not present in the healthy control sample. Despite these differences in temporal activation, however, direct comparison between patients and healthy controls showed only one region where between-group differences were significant: patients showed less activation at high memory load in a region of frontopolar cortex. These findings suggest that patients with mood disorders and healthy control subjects rely on similar frontoparietal control networks to support working memory task demand, and that patients also recruit temporal lobe structures to support performance.

On the recollection memory task we found significant differences in temporal lobe activation between patients and healthy controls; during recollection memory trials patients engaged posterior medial and lateral temporal regions primarily—regions that have been linked previously to episodic encoding (Eldridge et al., 2005), whereas healthy controls engaged anterior medial temporal regions primarily—regions that have been linked previously to episodic retrieval (Milne et al., 2011; MacQueen et al., 2003). Thus, findings from both tasks converge on differences in temporal lobe activation between patients and healthy

control subjects. It remains to be determined whether these differences reflect a compensatory or adaptive response in the patient group, however.

Our contrast of activation pre- versus post-training revealed the potential for functional change within brain regions involved in working memory and recollection memory task performance. On the n-back working memory task, we found increased activation in frontal control regions at high memory load, including lateral and medial prefrontal cortex and the dorsal cingulate. We also found increased activation in the right anterior hippocampus during recollection memory post-training, in almost exactly the same region that showed greater activation in healthy controls relative to patients with MDD in a previous report of recollection memory performance (Milne et al., 2011). These results provide some of the first evidence for functional change within frontal control networks and medial temporal lobe structures post remediation, and converge on our finding of improved performance on neuropsychological tests of working memory and delayed memory following training (Chapter 3).

Taken together, the findings presented within this thesis: i) confirm that there are differences in cognitive functioning between patients with BD and MDD, although these differences appear to be primarily in degree, and not pattern of deficit; ii) show that computer-assisted cognitive remediation has the potential to be widely beneficial for patients with mood disorders, particularly in domains of memory; and iii) demonstrate the potential for neuroplastic change in brain

regions involved in working memory and recollection memory following only 10 weeks of training. These findings may eventually lead to new advances in understanding and treating illness-related cognitive deficits. Moreover, the incorporation of cognitive remediation programs into comprehensive treatment plans may eventually translate into improved day-to-day functioning for patients with bipolar disorder and major depressive disorder who experience significant illness-related cognitive impairment.

5.1 Future directions of study

The evidence presented within this thesis represents one of the first comprehensive investigations of cognitive remediation in patients with mood disorders, and is intended to provide a strong basis for future work within this area. However, the extent to which firm conclusions can be drawn based on interpretation of the findings discussed here is limited by a lack of available research; further studies are necessary to confirm and extend these results.

For instance, the reasons why patients with BD tend to have a greater degree of impairment than those with MDD, particularly in domains of verbal memory and verbal fluency, remain to be addressed (Chapter 2). Patients with BD had a significantly higher medication burden than patients with MDD, and the extent to which the observed decrements can be attributed to overall medication burden, or to the effects of a particular medication, requires further investigation. This is a particularly important point to consider given the demonstrated

association between delayed recall performance and medication burden in our sample (Chapter 2). Another possibility is that deficits in verbal memory and verbal fluency in BD are trait-related, whereas deficits in these domains in MDD are state-related. Indeed, a recent review of cognitive functioning in patients with MDD found that verbal memory and verbal fluency were among the cognitive domains *most* sensitive to clinical state; improvements in mood were associated with improvements in task performance (Douglas & Porter, 2009). Whether deficits in verbal memory and fluency are state-dependent, particularly subtle, or restricted to a subgroup of patients with MDD—such as those with extensive illness burden (e.g., MacQueen et al., 2002) or higher medication load—requires further study, but may point to important neurobiological differences between these groups.

We determined that motivation was a positive predictor of improvement in memory and executive domains (Chapter 3), but whether motivation for treatment can be enhanced in a systematic way in patients with mood disorders remains to be addressed. Cognitive training interventions that incorporate intrinsically-motivating instructional techniques have been used in patients with schizophrenia with benefits to learning, motivation, and feelings of self-efficacy and achievement (Choi et al., 2010). Moreover, in patients with schizophrenia, intrinsic motivation is a critical intermediary in the relation between cognitive functioning and psychosocial functioning (Nakagami et al., 2010); this

emphasizes the importance of optimizing and maintaining intrinsic motivation over the course of a cognitive intervention. These will be important issues to address in future studies of cognitive remediation for patients with mood disorders, particularly if the intervention is used in community care or inpatient settings where symptoms of anhedonia may be more clinically relevant.

Conversely, if cognitive remediation is offered to outpatients as part of a comprehensive treatment plan, convenience of service—more so than intrinsic motivation—may be important to consider given the relative intensity of training demanded by the typical intervention. Cognitive remediation programs that offer the option of remote server access or web-based training could be used by patients from home, making participation more appealing for those with family obligations, full-time employment, or physical limitations. Further, it would be relatively simple to incorporate applications into these programs that provide instant feedback, monitor and track progress, and enable therapists and clients to interact remotely when issues arise. Programs such as these would also be a more cost-effective way to provide cognitive remediation within an outpatient setting; whether patients train at an on-site facility or at home, one therapist could manage a larger number of clients while providing the same level of supervision.

The fact that depressive symptom severity was a positive predictor of improvement in domains of attention and processing speed (Chapter 3) is another finding that requires further elucidation. We speculate that these gains actually

reflect a more pronounced response to the "activating" nature of treatment; however, studies that include active control groups to adjust for this type of effect are needed. The fact that depressive symptom severity did not *negatively* interfere with improvement also requires clarification; presumably, beyond certain intensity, depressive symptoms will interfere with any activating or beneficial effect of remediation. Given that the patients included in our sample were considered stable and subsyndromal, future studies that include acutely ill patients may be more informative in determining the impact of depressive symptoms on treatment. On balance, however, our findings do suggest that complete remission is not a necessary requirement for these interventions to be effective.

The main goal of any cognitive remediation intervention is to effect positive change in real-world functioning. Our results show evidence of some degree of generalization following CACR: improvements in overall cognitive functioning were associated with improvements in subjectively-assessed personal well-being; improvements in memory were associated with improvements in subjectively-rated cognitive functioning; and improvements in executive domains were associated with improvements in self-reported psychosocial functioning (Chapter 3). Although it must be conceded that *objective* change in real-world functioning is the ultimate demonstration of generalization, the importance of subjective improvement cannot be discounted. Subjectively-experienced change may further enhance motivation, self-confidence, and feelings of efficacy (Choi et

al., 2010; Eccles & Wigfield, 2002), and thus may be an essential intermediary for objective change to occur. Basic CACR programs that incorporate additional elements (i.e., strategy-based remediation techniques, supportive therapy, work skills training, or psychotherapy) as a means of scaffolding generalization have proven to be an effective means of optimizing the translation of cognitive gain to real-world skills in patients with psychotic disorders (see Wykes et al., 2011 for a meta-analysis). Further work will be needed to determine if this "combined" approach to training has similar utility for patients with mood disorders.

Our contrast of functional activation in patients with mood disorders pre- versus post-remediation found activation increases in frontal brain regions associated with working memory, and in medial temporal regions associated with recollection memory following training (Chapter 4). The fact that behavioural scores on the n-back task and recollection memory-process dissociation task were stable across visits raises questions about the exact nature of these changes, however. Specifically, the question of whether these changes reflect plasticity within domain-general frontal and temporal control networks versus plasticity within domain-specific or task-specific pathways requires clarification. A recent imaging study of cognitive remediation in patients with multiple sclerosis found increased activation in frontal, cingulate, and parietal cortices on a *trained* alertness task following remediation, but also on a more complex *untrained* attention task (Penner et al., 2006). The authors suggest that cognitive training

stimulated domain-general attentional networks, and that improved performance on the untrained task was due to enhanced focus and attentional control post-training. A recent meta-analysis of computer-assisted cognitive remediation in patients with schizophrenia also found that CACR exerts a "non-specific" beneficial effect to frontally-mediated control functions (Grynspan et al., 2011). Accordingly, we suspect that the observed activation increases post-training in our sample reflect remediation-induced neural reorganization or strengthening within domain-general frontal and temporal control networks, rather than change within the neural circuitry involved in working memory and recollection memory, specifically. Our finding of stable behavioural performance on the n-back task and recollection memory task across visits further supports this possibility; subtle changes in domain-general control networks are likely to influence task-specific measures of accuracy and reaction time to a lesser degree, particularly when the tasks in question have considerably different, or higher cognitive demands than the ones used during training. Further work is needed to determine whether a longer course of training or a "combined" approach to training can impact behavioural performance beyond tasks that are identical, or similar, to the training tasks.

An important question to consider following a cognitive intervention—particularly restitution-based interventions that emphasize repetitive practice—is the extent to which improvements on neuropsychological tests can be accounted

for by practice effects on the training tasks. Studies that use outcome measures that are identical, or similar, to the training tasks risk conflating practice with true gains in cognitive functioning. In the present study, several of the neuropsychological tests used to measure change were similar to the training tasks (e.g., digit span forward); however, the two neuropsychological tests that showed significant change following training (i.e., digit span backward and delayed recall) were not. The fact that patients reported subjectively-experienced gains in psychosocial functioning post-training is further confirmation that the observed neuropsychological improvements were more than just practice effects. Critically, our functional imaging findings also support this conclusion; the n-back task and recollection memory task used during scanning were unlike any of the tasks practiced during training. Therefore, the observed functional activation increases post-training cannot be fully accounted for by task-specific practice, and rather likely reflect generalization of gains at the neural level. Functional imaging studies that compare patterns of activation pre- and post-training on outcome measures that are identical to the training tasks versus outcome measures that are different may further elucidate the extent to which cognitive training impacts domain-specific or task specific, versus domain-general brain networks.

5.2 Conclusions

The central aim of this thesis was to examine the effectiveness of computer-assisted cognitive remediation for patients with mood disorders. The results presented here provide convergent behavioural and neural evidence to demonstrate the efficacy of this intervention for patients with BD or MDD. Addressing cognitive deficits early with a standardized treatment plan may prevent or minimize the impact of cognitive deficit on functional outcome and quality of life in these individuals. We were also able to identify several factors likely to impact response to remediation. This is an important issue, as the efficacy of any behavioural intervention depends largely on the appropriate selection of individuals for treatment. Identifying factors for clinicians to evaluate *before* recommending cognitive remediation, particularly in considering *when* during treatment an intervention might be most effective, would not only benefit patients, but would also ensure that resources are being used in the most cost-effective manner. Together, these novel findings contribute to a growing body of literature that shows cognitive remediation to be an effective cognitive management strategy across a range of psychiatric and neurological disorders. These programs have the potential to be widely beneficial for patients with mood disorders.

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