

**COGNITION-EMOTION DYSREGULATION IN
SCHIZOPHRENIA**

**EXPLORING COMPETITION BETWEEN COGNITIVE AND
EMOTIONAL RESPONSE CUES IN SCHIZOPHRENIA**

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

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McMaster University DOCTOR OF PHILOSOPHY (2014)
Hamilton, Ontario (Psychology)

TITLE: Exploring competition between cognitive and emotional
response cues in schizophrenia

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PAGES: xx, 270

ABSTRACT

The primary goal of this thesis was to characterize the parameters under which faulty emotion-cognition interactions emerge in Schizophrenia (SCZ). Its theoretical basis rests on neurobiological models specifying two related, yet independent, brain systems that govern how cognitive versus emotional processing impacts behaviour, and related research indicating differential impairment of the cognitive system in SCZ. These models predict that the disruptive impact of emotional information may be greatest when it is actionable and signals a competing response. However, most previous research on patients with SCZ has focused on the influence of extraneous emotional interference on primary cognitive processing. Thus, the central hypothesis guiding these experiments was that patients with SCZ will have the most difficulty prioritizing goal-directed, cognitive response cues in the face of countermanding emotional cues which impel an alternative response. Several different experimental tasks were used to interrogate this hypothesis, at both the behavioural and neural level. Overall, the results confirm that SCZ patients have difficulty prioritizing cognitive determinants of behaviour when emotion-laden information serves as an actionable and opposing response cue. However, the data are not conclusive; effect sizes were generally modest and results were not entirely consistent across studies. Therefore, while these experiments support dual-system neurobiological models of SCZ-related brain pathology, and provide interesting tentative suggestions for novel clinical approaches to treatment and remediation,

further research is needed to fully understand dysregulated emotion-cognition antagonism in this clinical population.

ACKNOWLEDGEMENTS

There are numerous people to whom I owe a tremendous amount of gratitude. Some were directly involved in the scientific process; others provided much-needed distraction away from science. Bruce Christensen - you provided both. Your mentorship and guidance over the past six years have been invaluable for my academic and professional growth. I could list all the specific ways this statement is true, but doing so would substantially lengthen an already-lengthy thesis. Although you're my "supervisor" on paper, I don't think this title is appropriate anymore. I now consider you to be a much smarter and more accomplished friend, and I look forward to many more years of pub and non-pub-based collaborations. I would also like to thank my committee members, Michael Kiang and Louis Schmidt, for your encouragement and enthusiasm since our first meeting together. I also must thank the numerous clinical advisors I've worked with along the way, namely Jelena King and Bruno Losier. You two laid the groundwork for my clinical training, and did so with a genuine and good-humored style that I've continued to model in my own clinical work. I would also like to acknowledge my teammate in this slightly unorthodox graduate career path, Justine Spencer. The long GO bus rides to and from York, the hateful trips on the QEW to and from Baycrest, and sadistic internship application process... all of these things would have been borderline intolerable without your companionship along the way. Thanks to my fellow intern and friend at MUSC, Bryan Heckman, for the indispensable support you provided in the final few weeks of my thesis writing. To the rest of my friends in Hamilton, Charleston, and

Saskatchewan – y'all are simply top notch. You've never failed to provide welcomed distraction from all things academia, which has kept me grounded throughout this journey. I could elaborate on this, but I should keep this document PG-13. Thank you also to my parents and brothers for your unconditional support since I entered university almost 10 years ago. The value of your support is immeasurable; it has kept me motivated to succeed and achieve since day one. Finally, a very special thanks to my wife, Sarah. Your patience and selflessness throughout our time together has been truly remarkable. Looking back, I'm amazed at how exceedingly well you've tolerated and *embraced* living with a perpetually busy (and mildly neurotic) graduate student. You are most definitely a keeper.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AEM	Accentuated emotional modulation
ANOVA	Analysis of variance
B1	Button 1
B2	Button 2
BA	Brodmann's area
BOLD	Blood-oxygen level-dependent
CBT	Cognitive-behavioural therapy
CDRT	Context-Direct Response Task
CERT	Context-Emotion Response Task
CEST	Cognitive-experiential self-theory
CI	Confidence interval
CMF	Conflict modulation failure
CMS	Common Mode Sense
COMT	Catechol-O-methyl transferase
CON	Congruent
DA	Dopamine
DCM	Dynamic causal modeling
DF	Directed forgetting
DG	Delayed gratification
DIS	Disorganized symptoms

DISC1	Disrupted in schizophrenia 1
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
DRL	Driven Right Leg
DSMF	Dual-stream modulation failure
DSM-IV-TR	Diagnostics & Statistics Manual of Mental Disorders, 4 th Ed. Text Revision
DTI	Diffusion tensor imaging
DTNBP1	Dysbindin
DTT	Dual cytoarchitectonic trends theory
DV	Dependent variable
EEG	Electroencephalography
EEM	Emotional enhancement of memory
eFSIQ	Estimated full-scale IQ
EMG	Electromyography
ERP	Event-related potential
EST	Emotional Stroop task
EXT	Externalizing
FVT	Face-vignette task
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder

GAD-67	Glutamic acid decarboxylase-67
HC	Healthy control
HF	High frequency
¹ H-MRS	Proton magnetic resonance spectroscopy
Hz	Hertz
IAPS	International Affective Picture System
INCON	Incongruent
INT	Internalizing
IOF	Index of facilitation
IOI	Index of inhibition
IQ	Intelligence quotient
IV	Independent variable
L1	List 1
L2	List 2
LF	Low frequency
LPP	Late positive potential
M	Mediator
MA	Moving away
MAM	Methylazoxymethanol acetate
MANOVA	Multivariate analysis of variance
MBSR	Mindfulness-based stress reduction
mGluR3	Metabotropic glutamate receptor-3

MINI	Mini International Neuropsychiatric Interview
MMN	Mismatch negativity
MPH	Motor process hypothesis
MRI	Magnetic resonance imaging
ms	Milliseconds
MSCEIT	Mayer-Salovey-Caruso Emotional Intelligence Test
MT	Moving towards
NAcc	Nucleus accumbens
NEG	Negative
NMDA	N-methyl-D-aspartate
NRG-1	Neuroregulin-1
OFC	Orbitofrontal cortex
PAI	Personality Assessment Inventory
PANSS	Positive and negative syndrome scale
PET	Positron emission tomography
PFC	Prefrontal cortex
POS	Positive
rCBF	Regional cerebral blood flow
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
REI	Rational/Experiential Inventory
RT	Response time
SCZ	Schizophrenia

SD	Standard deviation
SES	Socioeconomic status
SME	Stress management education
SPD	Schizotypal personality disorder
SPECT	Single photon emission computed tomography
TBF	To-be-forgotten
tb-fcMRI	Task-based functional connectivity magnetic resonance imaging
TBR	To-be-remembered
TTC	Time-to-collision
VMPFC	Ventromedial prefrontal cortex
WAIS-III	Wechsler Adult Intelligence Scale, 3 rd Edition
WHODAS	World Health Organization Disability Assessment Schedule
WM	Working memory
WRAT-4	Wide Range Achievement Test 4 th Edition

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Chapter 2: This chapter was a collaboration between myself, Dr. Bruce Christensen, and Kathy Smolewska. I was the lead on formulating and performing the experiments, analyzing the data, and preparing the manuscript. This chapter is current under review after one round of revisions in the *Journal of Neuropsychology*. The contents of this chapter is an exact representation of the latest version that has been submitted for review. No copyright has been assigned to this manuscript.

Chapter 3: This chapter was a collaboration between myself, Dr. Bruce Christensen, and Anuj Rastogi. I was the lead on formulating and performing the experiments, analyzing the data, and preparing the manuscript. This chapter has been accepted for publication to *Cognition and Emotion*. The contents of this chapter is an exact representation of the latest version accepted for publication. No copyright has been assigned to this manuscript at the time of final thesis submission.

Chapter 4: This chapter was a collaboration between myself and Dr. Bruce Christensen. I was the lead on formulating and performing the experiments, analyzing the data, and preparing the manuscript. This chapter has been published in *Psychological Medicine* and is reprinted here with permission from Cambridge Press (license # 3354830292312). The manuscript has been reformatted for consistency within the thesis with the exception of in-text citations, which are formatted according the submission guidelines of *Psychological Medicine*. A full citation of the article is provided on the cover page of this chapter.

Chapter 5: This chapter was a collaboration between myself, Dr. Bruce Christensen, and Dr. Michael Kiang. I was the lead on formulating and performing the experiments, analyzing the data, and preparing the manuscript. This chapter has been submitted for publication to *International Journal of Psychophysiology*. The contents of this chapter is an exact representation of the version of the manuscript that has been submitted for review. No copyright has been assigned to this manuscript.

ORGANIZATION OF THESIS

This document has been compiled as a “sandwich” thesis. As noted above, it contains four free-standing manuscripts which have been published (Chapter 4), are in press (Chapter 3), or have been submitted for publication (Chapters 2 and 5). The individual manuscripts are preceded by a General Introduction (Chapter 1) and followed by a General Discussion (Chapter 6). Please note that the sandwich thesis format has resulted in some minor redundancy between chapters. In particular, there is some overlap across the various Introduction sections, including the General Introduction. This is because the central hypothesis guiding the overall thesis also provides the conceptual foundation for each individual manuscript. Also please note that the “References” section that follows Chapter 6 provides references for the General Introduction and General Discussion chapters. References for the individual manuscripts (Chapters 2-5) are provided in self-contained Reference sections at the end of each manuscript.

CHAPTER 1

GENERAL INTRODUCTION

1.1 OVERVIEW OF THESIS

The purpose of this thesis was to characterize how patients with schizophrenia (SCZ) reconcile competing cognitive and emotional response cues when guiding behaviour. This investigation was motivated, in part, by inconsistencies within the SCZ literature pertaining to abnormalities in emotion-cognition interactions, as well as neurobiological models of SCZ that emphasize an imbalance between goal-directed, cognitive brain circuits and reactive, emotional circuits. This objective was examined at behavioural and neurophysiological levels using several different experimental paradigms. Each chapter includes relevant background and rationale for the individual experiments. In the present chapter, a more general review is provided, including a broad overview of SCZ, its associated cognitive and emotional processing deficits, and a review of literature on dual processing theories of cognition and emotion in healthy individuals and patients with SCZ.

1.2 SCHIZOPHRENIA: A GENERAL REVIEW

Schizophrenia (SCZ) is a complex mental illness that has attracted a vast amount of multidisciplinary research (greater than 100,000 studies, per PubMed). The volume of available data precludes an exhaustive review of the disorder within the present thesis. The purpose of this section (1.2.1 to 1.2.5) is to summarize some of the more empirically reliable findings derived primarily from meta-analyses and systematic reviews.

1.2.1 Clinical Features

SCZ is characterized by a range of cognitive, behavioural, emotional, and perceptual abnormalities, though no one symptom is pathognomonic of the disorder (American Psychiatric Association, 2013). Diagnosis is based on a combination of observable signs and/or reported symptoms that fall within the broader category of psychosis. Prototypical features of SCZ-related psychosis include delusions, hallucinations, thought disorder, grossly disorganized behaviour, and negative symptoms. *Delusions* are beliefs (often distorted, fantastic, or implausible) which are tenaciously held even when confronted with conflicting evidence. Delusional content can include thoughts of persecution, grandiosity, reference (the belief that seemingly random gestures or environmental cues are directed at oneself), or control (the idea that an alien force is inserting or withdrawing one's internal thoughts and feelings). *Hallucinations* are abnormal perceptual experiences that typically occur in the auditory and visual domain in the absence of an external stimulus. In patients with SCZ, these are often experienced as voices that provide commands or ongoing commentary on one's behaviour. *Thought disorder* is typically inferred from abnormal speech output, and is characterized by features such as tangentiality, derailment, loose associations, or incoherence. *Disorganized behaviour* can manifest in a number of ways, including psychomotor agitation, reduced goal-directed behaviour, bizarre posturing, and catatonia. Delusions, hallucinations, thought disorder, and disorganized behaviour are collectively referred to as positive symptoms. In contrast, *negative symptoms* are characterized by emotional unresponsiveness (e.g., anhedonia

and blunted affect), poverty of speech, social disengagement, and reduced motivation. A diagnosis of SCZ requires two or more of these prototypical features to be active for the majority of a one-month period (or less if successfully treated), with some signs of disturbance persisting for a continuous period of at least six months (American Psychiatric Association, 2013). There must also be evidence of functional decline in one or more major areas, such as education, interpersonal relations, work, or self-care. Cognitive processing deficits are also considered a core feature of disorder (Tandon, Nasrallah, & Keshavan, 2009); these will be reviewed in greater detail in a later section.

1.2.2 Onset and Course

The clinical course of SCZ consists of sequential phases that are continuous and often overlap. These include the premorbid phase, prodromal phase, progression phase, and the residual phase. The *premorbid phase* is characterized by subtle and nonspecific developmental abnormalities in childhood and adolescence (Tandon et al., 2009), including delays in linguistic and motoric development, poor academic achievement, and social isolation (Schenkel & Silverstein, 2004). This is followed by a *prodromal phase* characterized by sub-threshold psychotic symptoms, mood disturbance, cognitive impairment, social detachment, and functional deterioration (Corblatt et al., 1999). During the prodromal phase (which lasts ~5 years, Klosterkötter, Schultze-Lutter, & Ruhrmann, 2008) there is a gradual accumulation of positive symptoms culminating in the first psychotic episode, typically in late adolescence or early adulthood. This signals the beginning of the *progression phase* and

represents the clinical onset of SCZ. The first episode is marked by frank psychotic symptoms that can include a combination of the signs and symptoms outlined above (American Psychiatric Association, 2013). The modal age of onset is early-to-mid-20s for males and late 20s for females (McGrath, Saha, Chant, & Wilhem, 2008). The clinical course varies across patients, though the progression period typically follows a relapsing and remitting pattern. That is, patients experience recurrent psychotic episodes separated by periods in which positive symptoms abate and negative symptoms increase. Over the course of the progression phase, positive symptoms tend to become less severe, negative symptoms become more prominent, and day-to-day functioning continues to decline (Tandon et al., 2009). After several years, the cyclical pattern tends to stabilize, marking the onset of the *residual phase*, whereby acute symptomatic exacerbations become less frequent. The residual phase is similar to the prodromal phase in that patients are less likely to experience episodes of florid psychosis, but may continue to experience negative symptoms, mood disturbance, and poor functioning (Thara, 2004).

1.2.3 Etiology

Most contemporary models of SCZ pathogenesis include both hereditary and environmental components (i.e., two-hit hypothesis, Mednick et al., 1998). Support for this assertion comes from an extensive body of research that has documented multiple genetic and environmental risk factors associated with SCZ, with neither providing a complete causative explanation in isolation. A genetic contribution to SCZ was first illustrated by adoption studies in the 1960s (Heston, 1966; Kety et al.,

1968). This research investigated the risk of developing SCZ in adopted offspring of parents with the disorder who were raised by parents without SCZ versus adopted offspring of parents without the disorder who were raised by parents with SCZ. A risk for developing SCZ was only associated with the presence of SCZ in the biological parents. Subsequent studies examining concordance rates among monozygotic and dizygotic twins have strengthened the genetic argument. Among monozygotic twins, if one twin has SCZ, the risk for developing the disorder in the other twin is 40-50%. By contrast, among dizygotic twins, if one twin has the disorder, the risk of developing SCZ in the other twin is 10-15% (Sullivan et al., 2003; Tandon, Keshavan, & Nasrallah, 2008).

While such studies provide compelling evidence for biological heritability, they do not inform which chromosomal regions and genes are associated with increased risk for SCZ. For this purpose, researchers employ genetic molecular approaches. With respect to chromosomal regions, meta-analyses of genome-wide linkage studies have implicated 8p21-22 and 22-q11-12 as regions that may contain SCZ risk genes (Badner & Gershon, 2002; Lewis et al., 2003), though many additional regions have also been implicated (Harrison & Weinberger, 2005). Further analysis of these candidate regions using genetic association techniques have helped identify several putative susceptibility genes. Some of the more commonly cited genes include: NRG-1 (neuregulin-1; involved in neuronal migration, synaptogenesis, gliogenesis, and neurotransmission; Harrison & Law, 2006), DTNBP1 (dysbindin; required presynaptically for homeostatic modulation of

neurotransmission; Dickman & Davis, 2009), COMT (catechol-O-methyl transferase; catalyzes synaptic catecholamines, such as dopamine, epinephrine, and norepinephrine; Harrison & Weinberger, 2005), DISC1 (disrupted in schizophrenia 1; involved in neuronal proliferation and differentiation, cytoskeletal modulation, and membrane receptor trafficking; Weiner & Lubow, 2010), and mGluR3 (metabotropic glutamate receptor-3; presynaptic receptor involved in glutamate transmission; Harrison, Lyon, Sartorius, Burnet, & Lane, 2008). Interestingly, Harrison and Weinberger (2005) suggest that each of these genes may ultimately influence synaptic plasticity and the development/stabilization of cortical cytoarchitecture. This suggests that structural and functional abnormalities in neural microcircuitry may be central to SCZ pathogenesis (reviewed in more detail in section 2.4). It is important to note, however, that even for these more promising candidate genes, there is “a remarkable failure to replicate exactly the same markers” across studies (p.8, Tandon et al., 2008). Moreover, each of these genes in isolation account for a very small proportion of variance in liability for SCZ, thus supporting the assertion that it is a polygenic disorder with multiple genetic polymorphisms (Lichtermann et al., 2000).

Investigations of genetic risk factors shows that genes alone (or collections of genes) are not causative, but rather, confer increased vulnerability for the disorder. This implies that exogenous factors may be necessary to trigger onset of the disorder. Data from epidemiologic and animal research implicates a variety of pre-, peri-, and postnatal environmental risk factors. Maternal malnutrition during the first and early

second trimester has been linked to increased risk of SCZ and SCZ-spectrum personality disorders (Tandon et al., 2008). This association is likely mediated by micronutrient deficiencies, such as iron, folate, and vitamin D, as these have been linked to subsequent brain development (Piper et al., 2012). Maternal infection is another prenatal risk factor that has garnered considerable empirical support. Data from ecologic studies have shown elevated rates of SCZ in cohorts who were *in utero* during influenza epidemics (McGrath & Castle, 1995). Associations with other infectious agents have also been demonstrated, including rubella and *toxoplasmosis gondii* (Tandon et al., 2008). Subsequent animal research suggests that it is not exposure to infectious agents *per se* that confers greater risk, but rather, neuromodulatory effects associated with the body's natural immune response. For example, prolonged exposure to inflammatory cytokines (e.g., interleukins) *in utero* can alter local neural circuit properties by changing the complement of neuronal receptors, thereby influencing the potential for neural plasticity (Ashdown et al., 2006; Samuelsson, Jennische, Hansson, & Holmang, 2006). Such observations have contributed to the neurodevelopmental hypothesis of SCZ, which posits that some form of neural insult affects critical circuits in the brain during early development, resulting in clinical expression of the disorder when these circuits reach physiologic maturity (Weinberger, 1986). Several obstetric factors have also been shown to confer higher risk, including preeclampsia, emergency caesarean section, and fetal hypoxia (Cannon, Jones, & Murray, 2002). During childhood, head injury, parental separation or death, trauma or abuse, urbanicity, and migration are all documented

risk factors for developing SCZ as well (Tandon et al., 2008). Cannabis use during adolescence also increases risk of psychosis in adulthood (Piper et al., 2012).

1.2.4 Pathophysiology

1.2.4.1. Structural abnormalities. Structural imaging (e.g., magnetic resonance imaging, MRI) and post-mortem tissue analysis have revealed numerous macroscopic and microscopic brain abnormalities in patients with SCZ. Some of the more reliable macroscopic findings include reduced total brain volume, increased ventricular volume, reduction or reversal of cerebral asymmetry (e.g., smaller asymmetry in planum temporale), and basal ganglia enlargement (Keshavan, Tandon, Boutros, & Nasrallah, 2008). Grey matter reductions within the hippocampal formation have also been observed across the lifespan in SCZ, including in neuroleptic-naïve patients (Steen et al., 2006). Using diffusion tensor imaging (DTI) and fractional anisotropy (FA)¹, several studies have also revealed reduced connectivity in commissural structures (e.g., corpus callosum) and other white matter tracts (e.g., arcuate fasciculus and uncinate fasciculus) in patients with SCZ and their first degree relatives (Kubicki et al., 2007; McIntosh et al., 2006). In terms of microscopic abnormalities, one of the most robust neuropathological findings in SCZ is a reduction in neuropil² within the lateral and medial prefrontal

¹ Diffusion tensor imaging is an MRI technique that maps connections between different brain regions by measuring the diffusion of water molecules along white matter tracts. Fractional anisotropy is a scalar value between 0 and 1 that quantifies the degree of diffusion within a neural fiber, thereby indexing the structural integrity of white matter tracts.

² Neuropil refers to the dense network of neuronal processes where synaptic connections are formed (e.g., axon terminals, dendritic spines, and glial processes). Neuropil can be thought of as the synaptic scaffolding that supports interneuronal communication.

cortices (Selemon & Goldman-Rakic, 1999). For example, post-mortem tissue analysis of the prefrontal cortex (PFC) has shown reduced dendritic spine density and total basilar dendritic field size in layer V pyramidal cells in patients with SCZ (Black et al., 2004). Moreover, several reviews of SCZ neuropathology all support the conclusion that whole brain and regional volume reductions likely reflect reduced neuropil, not neuronal loss, perhaps due to elevated levels of synaptic pruning during development (McGlashan & Hoffman, 1997). A reduction in neuropil is in keeping with genetic studies of SCZ that implicate genes involved in the development and regulation of neural microcircuitry and synaptic signaling.

1.2.4.2. Neurotransmitter abnormalities. SCZ patients exhibit multiple neurochemical abnormalities. The dopamine (DA) hypothesis is perhaps the most influential and enduring theory of SCZ pathophysiology (Kapur & Mamo, 2003). Early iterations of the DA hypothesis proposed that hyperactivity within subcortical mesostriatal pathways resulted in excess stimulation of dopamine D₂ receptors, which then manifested clinically as psychotic (positive) symptoms. This assertion was initially borne out of the observation that first generation antipsychotic medications successfully alleviated psychotic symptoms by blocking striatal D₂ receptors. Further validation has come from the fact that second generation antipsychotics also block D₂ receptors (Stone, Morrison, & Pilowsky, 2007), while dopamine-enhancing agents (e.g., amphetamines) can induce psychotic symptoms (McKetin, McLaren, Lubman, & Hides, 2006). Moreover, using SPECT imaging,

Abi-Dargham et al (1998) demonstrated that greater amphetamine-induced positive symptoms correlated with increased dopamine release in patients with SCZ.

The classic DA hypothesis, however, is limited in that its explanatory power is confined to positive symptoms. Negative symptoms and cognitive deficits are generally resistant to the pharmacologic effects of D₂ receptor antagonists. With this in mind, indirect evidence supports the notion that a hypodopaminergic state within the PFC contributes to negative and cognitive symptoms in SCZ (Davis, Kahn, Ko, & Davidson, 1991; Weinberger, 1987). For example, preclinical studies have demonstrated a link between prefrontal DA transmission and cognitive functioning (Goldman-Rakic et al., 2000). This link is bolstered by the observation that carriers of the high-activity allele of the COMT gene (which codes for an enzyme involved in DA catabolism) display lower performance on various cognitive tasks compared to carriers of the low-activity allele (Goldberg & Weinberger, 2004). This is notable as the high-activity allele is associated with increased risk for SCZ (Wonodi, Stine, Mitchell, Buchanan, & Thaker, 2003), though this link may not be as strong as previously hypothesized (Fan et al., 2005; Williams, Owen, & Donovan, 2007). Thus, the DA hypothesis has been revised to suggest that a deficit in DA transmission at D₁ receptors in the PFC may underpin negative symptoms and cognitive dysfunction, whereas excess transmission at D₂ receptors in mesostriatal pathways may be related to positive symptoms.

More recent theories of neurochemical dysfunction in SCZ have highlighted the role of glutamate and gamma-aminobutyric acid (GABA). The glutamate theory

of SCZ (Olney & Farber, 1995) was derived from the observation that antagonists of the N-methyl-D-aspartate (NMDA) glutamate receptor, such as phencyclidine and ketamine, can lead to symptoms in healthy individuals that mimic those seen in SCZ, including delusions, hallucinations, thought disorder, and negative symptoms (Stone et al., 2007). Subsequent proton magnetic resonance spectroscopy (^1H -MRS) imaging studies indicate that regional glutamatergic abnormalities in SCZ most consistently show elevations in medial PFC and basal ganglia among medication naïve patients, perhaps reflecting a compensatory response to NMDA receptor hypofunction (Poels et al., 2014). Moreover, reduced glutamate receptor expression has been found in post-mortem tissue analysis in the PFC and hippocampus in patients with SCZ (Harrison et al., 2003). However, these studies have not been consistently replicated (Lewis & Gonzalez-Burgos, 2006) and clinical trials using glutamatergic agents have generally not been effective at ameliorating symptoms of SCZ (van Berckel, 2003). Thus, some have suggested that the glutamatergic system is not disrupted in isolation, but rather, may modulate, or be modulated by, the dopaminergic system (Stone et al., 2007).

Evidence for GABAergic dysfunction has come primarily from post-mortem studies. One of the most highly replicated pathophysiological findings in SCZ is reduced expression of glutamic acid decarboxylase-67 (GAD-67) and its mRNA precursor, both of which are central to the synthesis of GABA (Gonzalez-Burgos, Fish, & Lewis, 2011). Several studies have utilized *in situ* hybridization and found decreases in GAD-67 protein and mRNA expression in the dorsolateral PFC

(DLPFC; Akbarian et al., 1995) and anterior cingulate cortex (ACC; Woo et al., 2004). Interestingly, this reduction is often observed in a subpopulation of GABAergic interneurons that expresses the calcium-binding protein parvalbumin (Lewis, Curley, Glausier, & Volk, 2012). This is notable as parvalbumin-positive GABAergic neurons are critical to the production of synchronous gamma-frequency oscillations, which have been linked to working memory impairments in SCZ (Lewis & Gonzalez-Burgos, 2006).

1.2.4.3. Functional neuroimaging abnormalities. Studies using electroencephalography (EEG) have demonstrated reliable abnormalities in neuroelectric activity in patients with SCZ. Mismatch negativity (MMN) is an event-related potential (ERP) elicited in response to a deviant auditory stimulus embedded within a train of uniform stimuli. Reduced MMN amplitude is a robust finding in SCZ that may represent dysfunctional early stage sensory processing (Keshavan et al., 2008). Another ERP component, the P300, also has blunted amplitude and delayed peak latency in patients with SCZ (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004). This waveform is elicited using many different cognitive paradigms and is thought to reflect higher-level, post-sensory cognitive processing, such as target stimulus evaluation, attentional allocation, and memory encoding. However, abnormalities in the P300 may not be specific to SCZ as reduced amplitude is seen in other psychiatric disorders (Hall et al., 2007). SCZ-related abnormalities do not only present as reductions in ERP amplitude. The N400 is a negative-going ERP component elicited by meaningful stimuli that is reduced (i.e.,

amplitude is made less negative) when a preceding stimulus is semantically related to the eliciting stimulus (the N400 semantic priming effect; Kiang, Christensen, & Zipursky, 2011). Patients with SCZ exhibit deficient N400 semantic priming (i.e., *increased* N400 amplitude to the eliciting stimulus), suggesting they have difficulty using meaningful context to activate related concepts in semantic memory (Kiang, Kutas, Light, & Braff, 2008).

Functional MRI (fMRI) and positron emission tomography (PET) examine hemodynamic activity and glucose metabolism in the brain, respectively. A number of *in vivo* alterations in brain functioning have been consistently observed in SCZ patients using these two techniques. An oft reported finding is hypofrontal activation when patients are engaged in tasks that recruit the DLPFC (Keshavan et al., 2008). Meta-analysis of functional neuroimaging data has shown medium effect sizes for both activated and resting-state hypofrontal function (Hill et al., 2004).

Hypofrontality in SCZ was supported in a meta-analysis of critical nodes that mediate executive function (i.e., DLPFC and ACC; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Meta-analysis of fMRI data further suggests qualitatively similar prefrontal dysfunction in unaffected relatives and patients in the prodromal phase (Fusar-Poli et al., 2007). It is important to note, however, that hypofrontality is not a ubiquitous finding across frontal regions as multiple studies have also shown concurrent hyperfrontality in other PFC areas, possibly reflecting compensatory activity (Minzenberg et al., 2009). Moreover, studies have not consistently used the same task to induce frontal activity, ranging from working memory to verbal fluency

to visuospatial problem solving (i.e., Wisconsin Card Sorting Task). Therefore, some of the variability in findings may reflect different task demands (Keshavan et al., 2008). Less consistent abnormalities have also been observed in other regions, including the medial temporal lobe and auditory cortex (Keshavan et al., 2008). These inconsistencies have generated an interest in examining functional covariance across different regions in order to construct task-dependent models of neural network dysfunction (Dauvermann et al., 2013).

1.2.5 Epidemiology and Outcome

The estimated lifetime risk of developing SCZ is approximately 0.7% (Saha et al., 2005), with slightly higher risk found in males (McGrath et al., 2004) and among lower socio-economic classes (Tandon et al., 2008). The annual incidence rate of SCZ ranges from 8 to 40 per 100,000 per year (McGrath et al., 2004). While the overall incidence rate is relatively low compared to other mental disorders (American Psychiatric Association, 2013), SCZ is typically associated with more profound functional impairment. This includes increased likelihood of homelessness (Folsom et al., 2005) and unemployment (Thornicroft et al., 2004), with estimates of the latter suggesting less than one-fifth of patients achieve full-time employment (Tandon et al., 2009). In addition, approximately two-thirds of patients with SCZ will never marry, consistent with a general pattern of social disengagement (Tandon et al., 2009). Moreover, up to 80% of patients will abuse substances during their lifetime (mostly alcohol, nicotine, and cannabis), leading to poorer treatment outcomes and violence (Canadian Psychiatric Association, 1998). Patients with SCZ also have

increased mortality, with age-standardized estimates being approximately double that of the general population (Parks, Svendsen, Singer, & Foti, 2006). A considerable proportion of this increase (~25%) can be attributable to higher rates of suicide (Saha, Chant, & McGrath, 2007). At a societal level, SCZ carries a substantial financial burden, with annual direct and indirect costs in Canada estimated at \$6.85 billion in 2004 (Goeree et al., 2005).

These costs, both personal and monetary, highlight the need for a clearer understanding of predictors of functional outcome in SCZ. One of the central determinants of functional outcome in SCZ is cognitive impairment (Bowie et al., 2008). Composite measures of impaired cognition show a strong relationship with poor functional outcome, defined as community outcome, social problem solving, and psychosocial skill acquisition (Green, Kern, Braff, & Mintz, 2000). Associations have also been observed with specific cognitive domains. For example, structural equation modeling has shown that attention/working memory directly relates to work skills, executive functions directly relate to interpersonal behaviours, and processing speed directly relates to both of these outcomes, and participation in community activities (Bowie et al., 2008). A 21-year longitudinal analysis of children later diagnosed with SCZ also found that childhood IQ was a strong predictor of social outcome and service utilization later in life (Munro, Russell, Murray, Kerwin, & Jones, 2002). In addition, meta-analysis of objective (i.e., observable, clinician-rated) and subjective (patient satisfaction) quality of life measures found that cognitive variables only predicted the former (Tolman & Kurtz, 2012). These findings

collectively highlight the importance of research dedicated to characterizing and quantifying cognitive impairment in SCZ at multiple levels of analysis. Such research promises to uncover fundamental features of SCZ psychopathology and pathophysiology and, by extension, inform targeted treatment programs aimed at improving functional outcome and quality of life.

1.3 COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Cognitive impairment is considered a cardinal feature of SCZ (Heinrichs & Zakzanis, 1998). The most recent meta-analysis of cognitive functioning in patients with SCZ included over 470 controlled studies and confirmed moderate-to-large deficits across all domains, including: long-term memory (effect size = -1.14), short-term memory (-1.05), global intelligence (-0.96), premorbid intelligence (-0.57), language tasks (-0.99), executive function (-1.10), and attention (indexed by response time; 0.99) (Fioravanti, Bianchi, & Cinti, 2012). Cognitive deficits are also present at attenuated levels in the premorbid and prodromal phases of the illness and then worsen after the onset of psychosis (Bilder et al., 2006). Impairment persists and remains mostly stable throughout the progression phase of the illness, including in periods of positive symptom remission between psychotic episodes (Tandon et al., 2009). Moreover, only very modest improvements in cognitive functioning are observed with first and second generation antipsychotic treatment (Keefe et al., 2007). Interestingly, a seven-decade, cross-sectional study using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS;

Marder & Fenton, 2004) Consensus Cognitive Battery recently demonstrated that patients do *not* experience acceleration in cognitive aging during the residual phase, though very old patients (> 81 years) were not examined (Rajji et al., 2013).

Unaffected relatives of patients with SCZ exhibit a qualitatively similar pattern of cognitive dysfunction, albeit at a lesser magnitude of severity (Hoff et al., 2005), suggesting a genetic component to cognitive dysfunction in SCZ.

As noted earlier, cognitive impairment is an important predictor of functional outcome and objective quality of life in patients with SCZ. Consequently, treatments targeting cognitive dysfunction are imperative. However, most conventional therapeutic options have highlighted the treatment-refractory nature of cognitive impairment in SCZ. To address this gap, two major initiatives (MATRICS and Cognitive Neuroscience approaches to the Treatment of Impaired Cognition in Schizophrenia [CNTRICS], Barch et al., 2009) have been undertaken by the National Institute of Mental Health to develop effective treatments for cognitive impairment in SCZ. The MATRICS initiative established seven cognitive domains that are fundamentally impaired in SCZ and can serve as targets for new therapeutic agents. These include verbal learning and memory, visual learning and memory, working memory, attention and vigilance, processing speed, reasoning and problem solving, and social cognition. The CNTRICS is a complementary initiative that seeks to develop measurement approaches linking cognitive deficits in SCZ to specific neural systems, thereby facilitating translational research efforts aimed at identifying neurobiologic treatment targets. Both of these initiatives hold significant promise for

guiding empirical efforts aimed at developing new therapeutic strategies for improving cognitive function. A number of completed and ongoing clinical trials using the MATRICS Consensus Cognitive Battery have investigated the efficacy of potential cognitive-enhancing drugs for SCZ (see Keefe et al., 2013 for review). Unfortunately, the vast majority of studies completed to date have not been sufficiently powered to determine whether or not a particular treatment was efficacious. Moreover, the patient sample has been mostly comprised of older, chronic males who may be least likely to benefit from cognitive enhancing agents (Keefe et al., 2013). Thus, the utility of cognitive enhancing agents in SCZ remains to be seen.

An important challenge in understanding the nature of cognitive impairment in SCZ is that patients exhibit reliable deficits across a wide array of cognitive tasks. Although it is plausible that each of these deficits are subserved by distinct psychological and neural systems, this explanation is inconsistent with data that points to a more generalized cognitive deficit (Dickinson, Ragland, Gold, & Gur, 2008; Fioravanti et al. 2012). Structural equation modeling has demonstrated that a SCZ-related deficit in neuropsychological performance is largely mediated through a general ability factor that accounts for 63.3% of diagnosis-related variance (Dickinson et al., 2008). Only verbal memory (13.8%) and processing speed (9.1%) also accounted for direct effects, albeit at significantly reduced magnitude. Similarly, the most recent meta-analysis of cognitive deficits in SCZ indicates a generalized impairment that cuts across domains (Fioravanti et al., 2012). Moreover, individuals

considered to be at high risk for developing SCZ (i.e., in the prodromal phase) exhibit significantly impaired global cognitive performance compared to control subjects, suggesting generalized cognitive impairment may be a vulnerability marker for the disorder (Lencz et al., 2006).

These data collectively suggest that SCZ may be associated with a domain-general impairment. This raises the interesting possibility that cognitive impairment in SCZ can be largely attributed to dysfunction in one core mechanism. In this vein, Barch and Ceaser (2012) suggest that deficits in goal-directed, proactive cognitive control may be the common mechanism driving deficits across a subset of domains that are among the most robustly impaired in SCZ (i.e., working memory, context processing, and episodic memory). Proactive control is “a form of cognitive processing in which goal-relevant information is actively maintained in a form that optimally biases attention, perception, and action towards achievement of that goal” (p. 27, Barch & Ceaser, 2012). There is an internally-generated, anticipatory element to proactive control that helps guide goal-directed behaviour on the basis of current context or task demands (Braver, 2012). This contrasts with reactive control in which “attention is recruited as a ‘late correction’ mechanism that is mobilized only as needed” (p. 106, Braver, 2012). Braver (2012) posits that proactive control depends on maintaining an active representation of goal-related information in the lateral PFC via phasic dopamine-mediated signaling. Further, Braver has suggested that high conflict situations may result in a bias towards the proactive control mode. Therefore, clinical populations such as SCZ, which are characterized by

dopaminergic and prefrontal abnormalities, may exhibit diminished proactive control when confronted with an interfering stimulus that produces conflict, in turn relying more heavily on reactive control (Barch & Ceaser, 2012). Support for this theory is derived from several studies that corroborate the link between DLPFC dysfunction and deficits in proactive cognitive control in patients with SCZ (Barbalat et al., 2009; Minzenberg et al., 2009), neuroleptic-naïve patients (MacDonald et al., 2005), individuals at high clinical risk for developing SCZ (Fusar-Poli et al., 2007), and patients' non-psychotic first-degree relatives (MacDonald et al., 2009). An oft-encountered source of interference that could disrupt goal-directed, proactive control, and is of particular relevance to SCZ symptomatology, is emotion-laden events or stimuli. Indeed, emotionally arousing information can hold substantial motivational or biological significance that demands immediate processing, regardless of current context or task demands. An overview of research related to emotional processing in SCZ is detailed next.

1.4 EMOTION ABNORMALITIES IN SCHIZOPHRENIA

As with cognition, emotional processing is represented by multiple dimensions, including emotional expression, experience, perception, and regulation. Core aspects of SCZ symptomatology offer insight into possible areas of emotional dysfunction. Affective flattening (i.e., blunted emotional processing) is a common negative symptom that suggests an abnormality in emotional expression. Accordingly, two of the more well-replicated findings in SCZ are reduced prosodic

and facial expression. Meta-analysis of emotional prosody has shown significant impairment in patients versus healthy controls (effect size = -1.11). Moreover, the majority of studies examining emotional facial expression have found that individuals with SCZ, regardless of medication status, are less expressive in terms of frequency and intensity for both posed and spontaneous expressions (Treméau, 2006). Diminished facial and vocal expressions have also proven to be reliable at distinguishing patients with SCZ from other clinical groups, including depression, right hemisphere brain damage, and Parkinson's disease (Kring & Moran, 2008). Interestingly, although diminished observable facial expression is common in SCZ, studies using facial electromyography (EMG) indicate that patients nevertheless exhibit subtle, non-observable muscle contractions congruent with the emotional valence with which they are responding (Kring & Elis, 2013).

Another core negative symptom of SCZ is anhedonia (i.e., diminished capacity to experience pleasure), which suggests an abnormality in positive (hedonic) emotional experience. However, laboratory studies of in-the-moment positive emotional experience generally do not show differences between patients and controls. A meta-analysis of 26 emotion-induction experiments found that patients did not differ from controls when rating subjective hedonic reactions to stimuli (Cohen & Minor, 2010). A follow-up meta-analysis examining subjective arousal reported similar levels of arousal in response to pleasant and unpleasant stimuli between patients and controls (Llerena, Strauss, & Cohen, 2012). Similarly, several studies indicate mostly intact physiological responsivity to emotional stimuli (e.g.,

skin conductance and breathing rate; see Hempel et al., 2007; Hempel et al., 2005), as well as normal affective modulation of startle response in SCZ (Curtis et al., 1999; Kolet, Franken, & Tulen, 2005). Thus, despite the prominence of anhedonia in the clinical presentation of patients with SCZ, laboratory studies indicate that in-the-moment emotional experience is intact. Strauss (2013) has recently suggested that this discrepancy may partly reflect the dissociation between current (i.e., in-the-moment) and non-current (i.e., retrospective or prospective) reports of emotional experience. That is, reporting in-the-moment feelings necessitates access to experiential knowledge, whereas describing retrospective or prospective feelings requires access to previously acquired semantic knowledge (Robinson & Clore, 2002), with only the latter being diminished in SCZ (Strauss, 2013). This assertion is supported by experimental data showing selective deficits in maintaining emotional responsiveness after the removal of emotionally evocative stimuli in patients with SCZ (Kring, Gard, & Gard, 2011). Strauss' interpretation may also partly explain disrupted anticipation of hedonic or rewarding experiences in patients with SCZ (Barch & Dowd, 2010).

Deficits in emotional perception have also been extensively reported in SCZ using facial emotion and prosody recognition tasks. Concerning the former, meta-analysis of over 80 studies from 1970-2007 revealed a large deficit in facial emotion perception (Cohen's $d = -0.91$), with comparable effect sizes being observed for face emotion identification and discrimination (Kohler, Walker, Martin, Healey, & Moberg, 2010). However, an important caveat with these findings is the pronounced

general face processing deficit in SCZ, which begs the question of whether patients have difficulty perceiving emotional faces or faces more generally (Kring & Elis, 2013). Regarding prosody recognition, meta-analysis of 17 studies examining emotional prosody perception found an even larger deficit than emotional face processing ($d = -1.24$, Hoekert, Kahn, Pijnenborg, & Aleman, 2007). Deficits in prosody recognition may reflect aberrant fundamental acoustic processing, such as pitch discrimination (Matsumoto et al., 2006). It is interesting to note that studies examining implicit (incidental) versus explicit emotion perception using priming experiments have found relatively intact implicit processing of both faces (Linden et al., 2009) and prosody (Roux, Christophe, & Passerieux, 2010). Impairment in emotion perception (facial and vocal) has been linked to various aspects of psychosocial functioning, including social relationships, work functioning, and independent living (Irani, Seligman, Kamath, Kohler, & Gur, 2012; Hooker & Park, 2002; Kee, Green, Mintz, & Brekke, 2003). Thus, emotion perception impairment represents a robust finding in SCZ with implications for functional outcome.

Elements of positive symptomatology offer a different perspective on abnormalities in emotion perception and experience in SCZ. Psychosis (delusions and hallucinations) is known to be a significant source of emotional distress for patients with SCZ. Kapur (2003) has posited that psychosis is a disorder of aberrant salience, whereby innocuous events and stimuli are imbued with inappropriately heightened motivational or emotional significance via chronically dysregulated mesolimbic dopamine neurotransmission. Under normal circumstances, dopamine

release mediates the acquisition of salience towards motivationally important stimuli or experiences—the physiologic basis for reward processing. However, dysregulated dopamine transmission in SCZ may result in the “aberrant assignment of salience to external objects and internal representations” when it is not contextually warranted (p. 15). Over time (i.e., during the prodromal phase), there is a gradual accumulation of these aberrant experiences which continuously get interpreted by faulty cognitive mechanisms, resulting in abnormal, emotion-laden perception of benign events and stimuli, which, in turn, can develop into full-blown delusions and/or hallucinations (Kapur, 2003). Thus, the seeds of psychosis may be the aberrant assignment of emotional salience to otherwise neutral or benign events/objects; seeds that are planted much earlier than the first manifestation of psychotic symptoms.

Empirical support for the aberrant salience model comes from data showing emotional responses to neutral stimuli in patients with SCZ. Holt et al. (2006a) observed that delusional patients were more likely to classify neutral words as unpleasant compared to non-delusional patients and healthy controls—an effect they termed the “affective misattribution bias” (p.248). The previously cited meta-analyses of emotional experience also observed that patients with SCZ had stronger reported aversion (Cohen & Minor, 2010) and arousal (Llerena et al., 2012) to neutral stimuli. Neuroimaging research has confirmed inappropriate activation of amygdala-centered neural systems involved in fear in response to neutral stimuli in patients with SCZ (Hall et al., 2008; Holt et al., 2006b). Similarly, a recent meta-analysis suggested that the oft-reported finding of amygdala under-recruitment in response to negative

stimuli (reviewed by Aleman & Kahn, 2005) may, in fact, be due to elevated baseline amygdala activity in response to neutral stimuli (Anticevic, Repovs, & Barch, 2012).

Inherent within the aberrant salience and affective misattribution models is the notion of diminished emotion regulation. That is, abnormal emotional experiences and percepts operate unchecked by top-down mechanisms that should temper inappropriate emotional responding. Ochsner and Gross (2005) call this process “controlled regulation” and suggest that it facilitates the reinterpretation of a stimulus in order to alter one’s emotional response to it. In this way, the onset, duration, intensity, or content of an emotional response can be better aligned with one’s situational or behavioural context (Gross, 1998). There is growing evidence to suggest that effortful, controlled emotional processes are diminished in patients with SCZ. For example, patients have lower scores on the “Managing Emotions” component of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), which assesses adaptive emotion regulation ability (Kee et al., 2009). Patients also endorse less perspective taking (i.e., reappraisal) when regulating negative affect on self-report emotion regulation questionnaires (Rowland et al., 2013; van der Meer, van’t Wout, & Aleman, 2009). At a neural level, patients with SCZ and psychosis-prone individuals exhibit reduced functional connectivity between PFC and amygdala when instructed to cognitively reappraise negative images (Morris et al., 2012; Modinos, Ormel, & Aleman, 2010). Patients also show diminished alteration of ERP responses (i.e., late positive potential) to unpleasant images after being instructed to pre-appraise them in a more neutral light (Horan, Hajcak, Wynn, &

Green, 2013; Strauss, Kappenman, Culbreth, Catalano, Lee, & Gold, 2013).

Collectively, these data suggest a failure to instantiate top-down contextual regulation of emotional responding. In other words, the clinical expression of psychosis may reflect an impairment in patients' ability to integrate emotional and cognitive processing—i.e., cognition-emotion interactions.

1.5 COGNITION-EMOTION INTERACTIONS IN SCHIZOPHRENIA

Abnormalities in cognitive and emotional processing have been well-documented in SCZ when the two domains are examined independently. However, studies in cognitive and affective science over the past two decades have demonstrated that the integrative operation of emotional and cognitive processing is necessary for adaptive functioning (Ochsner & Phelps, 2007). Therefore, segregating these two processes in SCZ research risks overlooking potentially fundamental aspects of human behaviour and, by extension, overlooking something meaningful about SCZ psychopathology. In this context, investigations of emotion-cognition interactions in SCZ have become increasingly common, with much of this research seeking to characterize how cognitive processing is modulated or disrupted by extraneous emotional interference.

One commonly used approach in this regard focuses on the ability to suppress emotional distraction during working memory (WM)³ tasks. Considerable research

³ Working memory refers to a cognitive system in which transitory bits of information are held online (in mind), where they can be further processed and manipulated.

indicates that the amount of information one can hold and manipulate in mind is limited (Cowan, 2010); therefore, ensuring that goal-relevant information is prioritized is critical for optimal WM performance. In this context, Anticevic and colleagues (2011) examined blood-oxygen level-dependent (BOLD) response while SCZ patients and controls completed a visual delayed match-to-sample WM task⁴ in which participants were shown negative images, neutral images, or a fixation cross during the delay period. Behaviourally, controls showed stronger interference effects for negative distracters, whereas patients were equally distracted by negative and neutral images. Moreover, patients failed to recruit neural regions associated with interference resolution for both negative and neutral images, including the DLPFC and supramarginal gyrus. These data were interpreted as a general deficit in distracter filtering that was independent of emotion (Anticevic, Repovs, Corlett, & Barch, 2011). Diaz and colleagues (2011) performed a similar experiment and found that neither patients nor controls exhibited differential behavioural distraction effects as a function of emotion. However, emotional distracters elicited greater activation in bilateral orbitofrontal cortex, bilateral posterior cingulate cortex, right parietal cortex, and bilateral amygdala in controls, whereas patients with SCZ showed no difference in brain activation when processing emotional and neutral distracters (Diaz et al., 2011). Consistent with Anticevic et al. (2011), these results suggest that emotional

⁴ In the delayed match-to-sample task, participants are asked to encode a stimulus (sample stimulus), such as a shape or word. This is followed by a delay period in which no stimulus or a distracter stimulus is presented (maintenance period). A test phase then occurs in which the participant must indicate if a new stimulus matches the sample stimulus.

and neutral distracters led to comparable levels of interference within the SCZ group, perhaps reflecting aberrant salience of neutral content (Kapur, 2003).

Using a related paradigm, Habel and colleagues (2010) investigated WM performance in SCZ on an *n*-back task⁵ after introducing emotional interference in the form of a negative odour (fermented yeast). Negative odours elicited comparable performance decrements in both groups. At a neural level, however, negative versus neutral odours were associated with relative hypoactivation in dorsal ACC and dorsomedial PFC in patients with SCZ. These results are noteworthy as the dorsal ACC has been implicated in conflict detection and resolution, cognitive control, and attentional allocation (Bush, Luu, & Posner, 2000), and the dorsomedial PFC has been associated with autonomic regulation during emotional states (Miller & Cohen, 2001). Thus, this pattern of activity may reflect a deficiency in controlling the modulatory influence of emotion on cognitive processing in SCZ (Habel et al., 2010). A similar *n*-back study of adolescent-onset SCZ patients also found a general WM performance deficit in the negative odour condition that did not differ between patients in controls (Pauly et al., 2008). However, unlike Habel et al. (2010), patients exhibited dysfunction within a thalamocortical network that included the thalamus, angular gyrus, and precuneus in the negative odour condition. Taken together, these

⁵ In the *n*-back task, participants are shown a sequence of stimuli and asked to indicate if the current stimulus matches the one from *n* steps earlier in the sequence. The load factor *n* is used to manipulate task difficulty (higher *n* results in greater working memory load and task difficulty).

WM experiments reveal an inconsistent pattern of dysfunction in terms of SCZ-related susceptibility to emotional interference.

The emotional Stroop task (EST) has also been frequently used to index emotional interference. In the EST, participants are shown emotional or neutral words and are asked to name the ink colour in which the word is printed. Typically, emotional words slow down the colour identification process compared to neutral words—the emotional Stroop effect—presumably due to attention being allocated to the emotionally salient content of the words. Demily and colleagues (2010) observed that, although patients with SCZ were generally slower to respond, patients and control showed similar slowing for emotional versus neutral words (Demily et al., 2010). Comparable results have been found in unaffected relatives of patients with SCZ (Besnier et al., 2009) and positive schizotypy individuals (Mohanty et al., 2005). By contrast, Strauss and colleagues (2008) found that patients with deficit syndrome SCZ (i.e., patients with prominent negative symptomatology) exhibited reduced vulnerability to emotional interference for positive words on the EST, whereas non-deficit SCZ patients and controls exhibited an interference effect for both positive and negative words. This pattern was particularly evident in patients with significant anhedonia. The authors suggested that positive content failed to automatically capture the attention of deficit-syndrome SCZ patients, namely in those with elevated anhedonia, thereby mitigating the emotional Stroop effect (Strauss, Allen, Duke, Ross, & Schwartz, 2008). Similar results have been observed for SCZ patients with high anhedonia on an affective interference task (Martin, Becker, Cicero, & Kerns,

2013). Interestingly, patients with positive symptoms appear to be *more* vulnerable to emotional interference on the EST when the emotional stimuli embody threat or paranoia-related content (Bentall & Kaney, 1989; Besnier et al., 2011; Epstein, Stern, & Silbersweig, 1999). This has also been observed for negative versus positive and neutral words in positive schizotypy individuals (Mohanty et al., 2008). These findings are consistent with the notion that positive or psychotic symptoms reflect difficulty regulating the behavioural impact of affectively salient information (Kapur, 2003).

At a neural level, EST studies examining regional cerebral blood flow (rCBF) using PET imaging have found increased mesolimbic (periamygdala) activity in response to threat-related words in controls, whereas actively paranoid SCZ patients showed increased amygdala activity for both negative and neutral words. Further, paranoid patients exhibit reduced dorsal ACC activity in response to threat-related words which corresponded with increased behavioural interference effects compared to neutral words (Epstein, Stern, & Silbersweig, 1999). Positive schizotypy individuals exhibit a slightly different pattern of neural activity, with only negative words eliciting increased mesolimbic activity (amygdala and parahippocampal gyrus), as well as decreased activity in left DLPFC (Mohanty et al., 2008). Park and colleagues (2008) examined BOLD response using a modified version of the EST that required participants to judge the valence of an emotional word embedded within a picture that was congruent or incongruent with the word in terms of emotion category. In controls, incongruent trials elicited a relative deactivation of

limbic and paralimbic regions, including ventral ACC (commonly referred to as the affective division of the ACC; Bush et al., 2000) and ventromedial PFC (VMPFC). The authors suggest this may have reflected suppression of emotional processing, possibly due to top-down cognitive modulation elicited by the conflicting stimuli. Patients with SCZ did not show deactivation of the ventral ACC or VMPFC on incongruent trials. In addition, patients exhibited greater recruitment of the DLPFC on incongruent trials despite poorer task performance. In the context of greater behavioural interference effects compared to controls, this pattern of BOLD activity suggests that vulnerability to emotional perturbation in SCZ may reflect inefficient top-down modulation of limbic-driven, bottom-up emotional behaviour (p. 122, Park, Park, Chun, Kim, & Kim, 2008).

As with studies of emotional distraction and WM, there is partial disagreement across studies of SCZ-related dysfunction on the EST; however, the neuroimaging data consistently suggest abnormal frontolimbic activity when patients are confronted with emotional interference. This assertion is supported by data from several other attention-emotion paradigms. For example, Dichter and colleagues (2008) employed a forced choice visual oddball task that required participants to detect infrequent target circles embedded within a series of non-target stimuli consisting of infrequent aversive or neutral images and frequent squares. In healthy controls, a dorsal frontoparietal network comprised of DLPFC, dorsal ACC, and precuneus was activated in response to target events and suppressed in response to aversive images. By contrast, a ventral frontolimbic network comprised of the

amygdala, orbitofrontal cortex (OFC), and inferior frontal gyrus was activated in response to aversive images and suppressed in response to targets. Patients with SCZ, however, exhibited reduced dorsal and ventral network activation in response to target and aversive stimuli, respectively, as well as reduced suppression of dorsal and ventral networks in response to aversive and target stimuli, respectively (Dichter, Bellion, Casp, & Belger, 2008). Although these results suggest dysregulation between the dorsal executive-attention network and ventral emotion processing network in SCZ, the data only permit speculation regarding the direct functional connection between the two networks. Accordingly, Anticevic and colleagues (2012a) examined whole-brain amygdala task-based functional connectivity (tb-fcMRI) while patients and controls performed a perceptual decision making task with negative and neutral distraction. Controls exhibited strong negatively correlated tb-fcMRI between amygdala and DLPFC in response to negative versus neutral distracters. By contrast, SCZ patients demonstrated significantly weaker amygdala-DLPFC coupling in response to negative interference, suggesting an impaired capacity to instantiate top-down regulation of amygdala activity (Anticevic, Repovs, & Barch, 2012a). Similar results have been obtained when examining functional connectivity between DLPFC and amygdala in response to emotional distraction on a delayed match-to-sample WM paradigm (Anticevic, Repovs, Krystal, & Barch, 2012b).

In summary, it is evident that a consistent pattern of dysfunction has yet to emerge with respect to how emotional information perturbs cognitive processing in SCZ. The majority of behavioural findings suggest that patients are generally not

disproportionately vulnerable to extraneous emotional distraction compared to controls, though this appears to vary depending on prominent symptomatology. Specifically, higher positive symptoms (delusions and paranoia) may confer greater vulnerability to affective interference, whereas the opposite pattern occurs for patients with negative symptoms (anhedonia). On the other hand, neuroimaging data tend to show abnormal patterns of brain activation in SCZ patients more generally when confronted with emotion-laden distraction, particularly within fronto-limbic circuits. These disparate findings highlight the need for further research to ascertain the specific parameters under which cognitive processing may be disrupted by emotional content in SCZ.

1.6 DUAL-SYSTEM FRAMEWORK OF SCHIZOPHRENIA

Anticevic et al. (2012a) have speculated that SCZ-related vulnerability to emotional interference may hinge on the extent to which tasks engage amygdala-PFC coupling. They suggest the PFC serves to down-regulate amygdala responsiveness to emotional stimuli, particularly when the emotional stimulus is task-relevant and can be used to guide behaviour (i.e., *not* simply an extraneous distraction). Therefore, susceptibility to emotional interference in SCZ may reflect weaker amygdala-PFC coupling on tasks in which the emotional information is *task-relevant* and *actionable*. Consistent with this assertion, several dual-system models of SCZ psychopathology and pathophysiology predict that the disruptive impact of emotional material may be greatest when it directly opposes or competes with goal-directed cognitive processing

by impelling an alternative response (Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003; Speechley & Ngan, 2008).

1.6.1 Overview of Dual-System Theories

Dual-process theories of behaviour have commonly appeared in the psychological literature over the past four decades. In the 1970's, Schneider and Shiffrin (1977) outlined a dichotomous theory of attention comprised of automatic and controlled processing. In this model, automatic processes operate independently of volitional control by the individual and are thought to reflect “the activation of a sequence of nodes that nearly always becomes active in response to a particular input configuration” (p. 526, Schneider & Chein, 2003). In contrast, controlled processes are slow, effortful, and represent “a temporary sequence of nodes activated under control of, and through attention by, the subject” (p. 2, Schneider & Shiffrin, 1997). This dual process mechanism is evolutionarily advantageous as the controlled stream allows for successful planning and execution of goal-directed behaviour, whereas the automatic stream facilitates high-speed, low-effort processing of frequently encountered or motivationally significant external stimuli (Schneider & Chein, 2003). In parallel to Shiffrin and Schneider's research, Daniel Kahneman and Amos Tversky investigated biases in probabilistic judgment and distinguished between two modes of thought underpinning judgment and decision making. *System 1* is intuitive, effortless, stimulus-driven, habitual, and emotional, while *System 2*, is analytic, deliberative, effortful, and internally-generated (Kahneman, 2003). Generally, these systems operate in concert to promote adaptive functioning; however, if conflict

emerges between the two systems, such as when an automatic computational process is engaged when not situationally appropriate, System 2 can override System 1 to contextually regulate one's actions (Stanovich & West, 2000).

Expanding on these early models, Epstein (1994) put forth a dual-system framework of personality termed cognitive-experiential self-theory (CEST). Similar to previous theories, CEST posits that information is processed using two distinct, yet interactive systems: an experiential/intuitive system and a rational/analytic system. The experiential system is rapid, preconscious, requires minimal cognitive effort, is driven by associative learning, and is intimately tied to emotion. It is evolutionarily ancient and operates according to the hedonic principle of "pursuing positive affect and avoiding negative affect" (p. 298, Epstein, 2010). By contrast, the rational/analytic system is conscious, effortful, demanding of cognitive resources, and affect-free. It has a relatively brief evolutionary history and is, therefore, a uniquely human attribute (Epstein, 2010). These two systems can act either sequentially or simultaneously in a bidirectional manner in order to guide thought and behaviour. What distinguishes CEST from previous dual-process frameworks, however, is its attempt to explain one's personality architecture in terms of the relative dominance of one system or the other. For example, the Rational/Experiential Inventory (REI) is a self-report measure developed to characterize the advantages and disadvantages of experiential/intuitive versus rational/analytic thinking styles (Epstein, Pacini, Denes-Raj, & Heier, 1996). Some of the positive qualities found to be associated with a predominantly experiential

thinking style are creativity, empathy, appreciation of aesthetics and arts, and open-mindedness. However, it has also been linked to authoritarianism, inflexible or stereotyped-thinking, superstitious belief systems, and naïve optimism (Epstein, 2010; Kemmelmeier, 2009; Norris & Epstein, 2011). Positive qualities associated with a rational/analytic thinking style include realistic thinking, low neuroticism, high intellectual performance, and conscientiousness, though this may also be linked to a dismissive attachment style (Epstein, 2010).

1.6.2 Dual-System Antagonism

One of the first dual-process models to emphasize an *antagonistic* relationship between cognition and emotion was the “hot-cool” system of self-control outlined by Metcalfe & Mischel (1999). This two-system theory was derived from empirical observations using a delayed gratification (DG) paradigm. In this paradigm, the experimenter presents a child with an appetitive stimulus (e.g., one piece of candy) and offers the following ultimatum: either wait until the experimenter returns from an absence of unspecified length and receive extra candy, or ring a bell to have the experimenter return immediately, but only receive the one original piece of candy. In this way, a goal-directed behaviour (delaying gratification for a greater reward) and an emotion-driven behaviour (taking the immediate reward) are antagonistic to one another. Although most children prefer the larger reward and initially attempt to wait, they typically succumb to temptation during the delay period and opt for the immediate lesser reward by ringing the bell. From these experiments, Metcalfe & Mischel (1999) postulated the existence of a “hot” emotional system of self-control

which is fast, impulsive, reactive, affect-driven, and under stimulus control, as well as a “cool” cognitive system which is slow, reflective, strategic, and emotionally neutral. In other words, the cool system governs our internally-generated, controlled behaviours (exercising restraint during the DG paradigm) and the hot system oversees reflexive responding to emotionally meaningful stimuli (succumbing to appetitive temptation during DG paradigm).

The DG paradigm has been adapted to adult samples by offering actual or hypothetical monetary rewards. These studies are grounded in the assertion that a remote monetary reward must hold greater subjective value in order to be preferred over a more temporally proximate one (Heerey, Robinson, McMahon, & Gold, 2007). This subjective value is captured by the delay discounting function, which describes the “decrease in the subjective value of a commodity as a function of the amount of delay in receiving that commodity or reward” (Bickel & Johnson, 2003). Delay discounting can be quantified using a procedure in which one must make a choice between two rewards separated in time. The value of one reward is systematically varied until the participants’ preference switches from the proximate, smaller reward to the remote, larger reward (Bickel et al., 2007). Thus, the more a person discounts or decreases the subjective value of later rewards, the more impulsively they will respond. Functional neuroimaging data show greater activity in DLPFC and posterior parietal cortex when individuals choose the delayed reward, whereas increased activity in paralimbic and ventromedial regions is associated with more impulsive responding (McClure, Laibson, Loewenstein, & Cohen, 2004). These

data have contributed to the development of neuroeconomic theories of decision-making which emphasize competing neural systems related to delayed choices (i.e., the dorsal executive system) and immediate or impulsive choices (i.e., the ventral/limbic impulsive system; Bickel et al., 2007). Given that patients with SCZ consistently show compromised DLPFC function, it stands to reason that they would be less likely to choose delayed rewards. Indeed, Heerey et al. (2007) observed that patients discounted remote rewards significantly more than controls, suggesting dysregulation between the two neural systems in the form of impaired dorsal executive system function. Consistent with this notion, certain neurobiological models of SCZ predict an imbalance between reactive, automatic brain circuits versus goal-directed, cognitive circuits (Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003).

1.6.3 Dorsal Deficiency Model of SCZ

Christensen and Bilder (2000) and Giaccio (2006) used evolutionary cytoarchitectonic theory as a conceptual framework for considering SCZ neuropathology. The dual cytoarchitectonic trends theory (DTT, Sanides, 1969) posits that mammalian neural architecture has evolved along two distinct, yet interactive pathways: the dorsal (i.e., archicortical) trend and ventral (i.e., paleocortical) trend. On the basis of cross-species cytoarchitectonic and cortical mapping studies (Pandya & Yeterian, 1985; Sanides, 1969), it has been shown that the dorsal trend originates in brain structures homologous to the hippocampal formation in mammals, whereas the ventral trend emanates from structures

homologous to the pyriform cortex and adjacent amygdalar complex. Projections within these pathways reflect successive stages of cytoarchitectonic development (Yeterian, Pandya, Tomaiuolo, & Petrides, 2012). The dorsal trend proceeds both pre- and post-Rolandically along dorsal-medial aspects of the cerebrum, including the hippocampus, dorsal ACC, DLPFC, and inferior parietal lobule. The ventral trend proceeds pre-and post-Rolandically along ventral-lateral aspects of the cerebrum and includes structures such as the amygdala, orbitofrontal cortex, ventrolateral PFC, insula, and much of the temporal cortex (Giaccio, 2006; Yeterian et al., 2012). This duality is conserved in the phylogenetic progression from fish to reptiles to primates, as the cerebral cortex evolved from three to six layers (Bilder, 2012). Functionally, the dorsal stream is responsible for planning and organizing actions in time and space, as well as executing prospective, internally-generated control functions based on contextual or task-relevant factors. By contrast, the ventral stream is specialized for identifying and assigning meaning to stimuli, as well as guiding arousal-based, reactive behaviour to emotionally or motivationally significant novelties in the external environment (Bilder, 2012; Christensen & Bilder, 2000; Giaccio, 2006). This dichotomous functional characterization is highly consistent with the dual-process models of information processing described above, as well as the dorsal-ventral neuroanatomical organization outlined in neuroeconomic theories of information processing (Bickel et al., 2007).

Using the DTT as a conceptual framework, Christensen and Bilder (2000) and Giaccio (2006) have postulated that dorsal stream deficiencies underlie many aspects

of the clinical phenomenology associated with SCZ. For example, Frith's (1992) neuropsychological model of SCZ centers on deficits of "willed action" and "willed intention," both of which are subserved by the dorsal trend. Willed actions are volitional acts (motor or otherwise), whereas willed intentions are the conscious representations of volition which signal that our acts are under voluntary control. In Frith's model, deficits of willed action should result in several consequences that align with fundamental symptoms of SCZ. These include (1) reduced initiation of mental and physical activity (negative symptoms), (2) attenuated voluntary inhibition of inappropriate responses (inappropriate affect and distractibility), and (3) failure to terminate responses (behavioural or cognitive perseveration) (Christensen and Bilder, 2000). Failures in willed intention may also explain key SCZ symptoms. For instance, considerable research shows that willed intentions cause both a motor response and a corollary discharge which labels our actions as internally generated (Miall & Wolpert, 1996). When this system is damaged, volitional acts are experienced as alien and can give rise to delusions of control (Frith & Johnstone, 2003). Such deficits can also explain auditory-verbal hallucinations, whereby internal speech is interpreted as externally generated.

Specific defects to the dorsal trend are also consistent with previously identified macro- and microscopic abnormalities that disproportionately involve dorsal-medial neural regions, such as the hippocampus (Lodge & Grace, 2011), anterior cingulate cortex (Fornito, Yucel, Dean, Wood, & Pantelis, 2009), DLPFC (Crespo-Facorro, Barbadillo, Pelayo-Teran, & Rodriguez-Sanchez, 2007; Selemon,

Rajkowska, & Goldman-Rakic, 1995), and dorsal visual system (Butler et al., 2005). Reduced functional capacities mediated by these structures have also been reliably observed in individuals with SCZ, including visually-guided grasping behaviour (e.g., King, Christensen, & Westwood, 2008), working memory (Lee & Park, 2005), context processing (Cohen, Barch, Carter, & Servan-Schreiber, 1999), delay discounting (Heerey et al., 2007), conflict monitoring (Kerns et al., 2005), and detection of peripheral visual targets (Elahipanah, Christensen, & Reingold, 2010). Moreover, a recent review of SCZ neurocognition argues that executing internally-generated, proactive control processes is a core dysfunction in SCZ that drives impairment across multiple cognitive domains, including context processing, working memory, and episodic memory (Barch & Ceaser, 2012). Importantly, populations characterized by deficient proactive control may exhibit increased reliance on reactive control processes (Barch & Ceaser, 2012). Thus, convergent lines of evidence within the DTT framework offer support for diminished influence of goal-directed, cognitive brain circuits relative to reactive, emotion-driven circuits in SCZ. This imbalance predicts that when emotional and goal-directed behaviours are in conflict, patients will have selective difficulty instantiating goal-directed behaviours and, instead, may act on the basis of emotional response cues.

1.6.4 Corticolimbic Gating Dysfunction in SCZ

Grace (2003) offers a complementary account of dysregulated emotion-cognition antagonism derived from animal models of SCZ. Following a series of single neuron recording studies in rodents, Grace and colleagues posit that the

hippocampus and amygdala provide facilitatory gating influences over information flow from the PFC at the level of the nucleus accumbens (NAcc). In this model, the PFC provides multiple potential response patterns by which it drives goal-directed action. The most effective plan is then selected within the NAcc in accordance with modulating inputs from either the hippocampus or amygdala. Under normal conditions, the hippocampus selects a response output based on the task demands or past experience with the stimulus (i.e., context). However, in the face of affectively salient stimuli, the amygdala can override the hippocampus and direct behaviour to effectively deal with the emotional or motivationally significant material. The NAcc-selected response is then passed back to the PFC for its enactment (Grace, 2003). Thus, these two gating influences work in concert to select the most appropriate and adaptive behaviour in a given situation.

In SCZ, however, this circuitry is presumed to be dysregulated. By administering a developmental mitotoxin (methylazoxymethanol acetate, MAM) to pregnant rats at gestational day 17, neurodevelopment of the ventral hippocampus is selectively disrupted (Lodge & Grace, 2009). This is critical as ventral hippocampal lesions are a facet of SCZ-related neuropathology that has garnered considerable empirical support (Tseng, Chambers, & Lipska, 2009). When tested as adults, the MAM-treated rats display multiple anatomical and behavioural abnormalities consistent with SCZ, including thinning of the limbic cortices without neuronal loss, orofacial dyskinesias, heightened response to an amphetamine challenge, and altered sensory gating (Grace, 2012). At a neural level, a primary consequence of this

developmental perturbation is that the hippocampus fails to properly facilitate PFC throughput. Instead, the amygdala drives the PFC activity in an antagonistic or competitive fashion (Grace, 2003). Thus, the system is biased to react based on affective inputs from the amygdala. Consequently, contextually-driven responding is presumably diminished and may be replaced by impulsive responding based on emotional or motivationally significant novelties in the environment (Grace, 2003).

Taken together, both the evolution-centered dorsal deficiency model and the cortico-limbic gating model predict diminished influence of goal-oriented, cognitive brain circuits relative to affect-driven, responsive brain circuits in patients with SCZ. This dysregulation offers insight into the specific parameters under which faulty emotion-cognition interactions might emerge and, by extension, provides a theoretical framework for certain behavioural predictions. Specifically, when emotional and goal-directed response determinants are put in direct conflict, goal-directed, cognitive responding should be diminished and may be replaced by reactive, emotion-driven responding. This prediction, however, has yet to be tested and validated in a human clinical sample. Therefore, the current thesis tests the central hypothesis that **patients with SCZ have disproportionate difficulty prioritizing goal-directed, effortful, cognitive response cues in the face of countermanding emotional cues which impel an alternative response**. Studies designed to elucidate these competing influences on behaviour will enhance our understanding of the behavioural mechanisms of SCZ psychopathology and may further validate the neurobiological models reviewed here.

1.7 SUMMARY OF CHAPTERS

The central hypothesis was examined at both behavioural and neural levels of analysis using a variety of experimental paradigms. Chapter 2 examined how patients reconcile direct competition between contextual and emotional response cues. This experiment employed a novel paradigm developed in our lab called the Context-Emotion Response Task (CERT) that is grounded in the motor process hypothesis (MPH). The MPH argues that arm flexion is an approach-motivated action in response to appetitive stimuli and arm extension is an avoidance-motivated action in response to aversive stimuli. With this in mind, the CERT used emotional pictures to elicit these motor responses using a three button array extending out from the participants midline. Viewing negative images signaled arm extension (i.e., pressing the distal button) and positive images signaled arm flexion (i.e., pressing the proximal button). Importantly, the CERT introduced instructional cues which necessitated responding either in-line with (green picture border) or in opposition to (red picture border) this inherent motor bias on a trial-by-trial basis. In this way, we were able to directly examine if patients with SCZ had disproportionate difficulty overriding emotional response determinants (i.e., emotional pictures) when cued to do so by an opposing and task-appropriate contextual cue (i.e., border colour). This experiment also included a non-emotional task that was analogous to the CERT called the Context-Direction Response Task (CDRT). Participants viewed neutral images that appeared to be either moving away (zooming out) or moving towards (zooming in)

them. In the congruent condition (green border), participants pressed the distal button for images that appeared to be moving away and the proximal button for images that appeared to be moving towards. This response mapping was reversed in the incongruent condition (red border). Thus, the button set-up was the same as in the CERT; however, the discrimination was based on the movement of the images, rather than their emotional category. The CDRT was included to determine whether patients with SCZ have selective difficulty overriding emotional incongruency, or whether they simply exhibit a general incongruency deficit.

Chapter 3 examined how patients reconcile direct competition between automatic versus effortful emotional response cues. A paradigm called the face-vignette task (FVT) was used in which participants were shown an emotional face paired with situational vignettes that conveyed a different emotion. For example, a face depicting fear might be paired with a vignette that conveyed pain. Assuming that the face stimulus represented the subject of the vignette, participants were asked to indicate what emotion the person was feeling on each trial. In this way, each response was based on facial information (i.e., automatic emotional processing), situational information (i.e., effortful emotional processing), or neither (random responding). This task has been used once before with a SCZ sample, though several methodological issues warranted replication and extension. This included experimental and statistical modifications to better account for variance attributable to working memory demands, reading comprehension ability, and basic emotional face processing ability.

Chapter 4 examined how patients reconcile direct competition between conflicting memory cues that reflected either explicit tasks demands or an automatic emotional response. This experiment used a list-method, emotional directed-forgetting (DF) paradigm. In general, DF experiments demonstrate that individuals are able to intentionally forget certain information in favour of target information when cued to do so. We employed a list-method variant whereby participants are shown a set of items to study for later recall (i.e., list 1). In the forget condition, they are instructed to forget those items in favour of a subsequent set of study items (i.e., list 2). At recall, participants are asked to recall items from both lists. The forget cue attenuates recall of list 1 and enhances recall of list 2. Successful forgetting of items that preceded the forget cue has been attributed to retrieval inhibition. By including emotional words, this study placed the well-characterized emotional enhancement of memory effect (EEM) in direct opposition to forget cue-induced inhibition. In other words, strategic inhibition must override prepotent emotional memory enhancement for successful task completion.

Chapter 5 is an extension of the emotional DF study from Chapter 4. Given that there are several alternative hypotheses that could account for aberrant emotional DF in SCZ, this task was adapted to an ERP paradigm to better elucidate the underlying cognitive and neural processes. At a broader level, this experiment was also completed because the previous 3 experiments provided only an inferential window into the neural substrate that underpins emotion-cognition competition in SCZ. A more direct window into the associated functional neurobiology was,

therefore, a logical extension of these behavioural experiments. The specific task parameters for this experiment varied slightly from its behavioural counterpart in Chapter 4. We used an item-method variant, rather than a list-method, as this has been previously employed in ERP research. In the item-method variant, participants are cued to either remember or forget immediately after each item is presented. The general DF effect remains the same: during the recognition phase, hit rate for to-be-remembered (TBR) items is typically much higher than for to-be-forgotten (TBF) items. Two cognitive mechanisms thought to underpin this effect are selective rehearsal of TBR items and/or active inhibition of TBF items.

Chapter 6 provides a general summary of the main findings from the individual experiments. The implications for SCZ neurobiology and neural network dynamics, psychopathology, and treatment are then discussed. The last portion of this chapter identifies potential limitations of the current thesis that can be leveraged to guide future investigations.

CHAPTER 2

INHIBITING REACTIONS TO EMOTIONAL VERSUS NON-EMOTIONAL RESPONSE CUES IN SCHIZOPHRENIA: INSIGHTS FROM A MOTOR PROCESS PARADIGM

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ABSTRACT

Recent models of schizophrenia suggest deficient use of contextual response cues when confronted with countermanding emotional cues. It is important to clinically validate these models by testing patients diagnosed with schizophrenia on tasks with competing emotional and contextual response determinants. Control and schizophrenia groups completed a novel task that elicited motor responses consistent with, or in opposition to, prepotent emotional actions (i.e., approach vs. avoidance). An analogous non-emotional task was also used to examine cue-conflict impairment more generally. The groups demonstrated statistically equivalent performance decrements on incongruent versus congruent trials on both tasks. However, within the schizophrenia group, the incongruency effect was significantly greater in the emotional versus non-emotional task. These data suggest that, while patients with schizophrenia were able to employ contextual response cues to override competing emotional responses, they were slower to resolve emotional versus non-emotional response conflict. When patients were subdivided according to the presence of absence of disorganized symptoms, this effect was confined to patients with disorganized symptoms.

2.1 INTRODUCTION

Recent accounts of schizophrenia (SCZ) psychopathology have highlighted dysregulation between emotional and cognitive processing (e.g., Anticevic & Corlett, 2012). Most studies that have examined emotion-cognition interactions in SCZ have focused on patients' susceptibility to emotional distraction. The data in this regard are equivocal, with some studies suggesting greater vulnerability to emotional distraction (e.g., Bentall & Kaney, 1989; Dichter, Bellion, Casp, & Belger, 2010; Mohanty, Herrington, Wenzel, Webb, & Heller, 2005; Park, Park, Chun, Kim, & Kim, 2008; Strauss, Allen, Duke, Ross, & Schwartz, 2008), and others showing no differential susceptibility (Anticevic, Repovs, & Barch, 2012; Anticevic, Repovs, Corlett, & Barch, 2011; Demily, Attala, Fouldrin, Czernecki, & Ménard, 2010; Diaz et al., 2011; Gopin, Burdick, DeRosse, Goldberg, & Malhotra, 2011). Anticevic et al. (2012) have speculated that SCZ-related susceptibility to emotional distraction may reflect abnormal amygdala-prefrontal cortex coupling that is most apparent on cognitively demanding tasks that utilize actionable emotional information. In a similar vein, the current study hypothesizes that the deleterious impact of emotional material in SCZ may be greatest when it directly opposes cognitive or contextual cues that impel an alternative response.

The rationale for this assertion is derived from models of SCZ psychopathology that emphasize an imbalance between the influence of emotional and contextual response cues. For example, Speechley and Ngan (2008) have outlined a dual-stream model of reasoning that extends the two-system framework of

information processing first described by Kahneman and Tversky (Kahneman, 2003). In this model, reasoning is governed by interactions between a “fast, intuitive, and automatic” stream (i.e., Stream 1) and a “slow, conscious, and deliberative” stream (i.e., Stream 2) (p. 1210; Speechley & Ngan, 2008). Emotional stimuli initially bias decision making towards Stream 1. However, should conflict arise between the two streams, healthy individuals will typically recruit Stream 2 in order to “initiate a more thorough consideration of all available evidence” (p. 1212). This implies that Stream 2 can implement corrective modifications when behaviour is erroneously based on Stream 1. Speechley and Ngan (2008) suggest that SCZ is characterized by a failure to modulate conflict between Streams 1 and 2 such that Stream 2 is no longer preferentially recruited during periods of conflict, leaving Stream 1 to predominate during heightened emotional states. Thus, when conflicts involving emotional material arise, individuals with SCZ may exhibit a breakdown in normal regulation of inputs to decision-making, thereby grounding decisions in emotion rather than logic.

Commensurate dual-stream models of SCZ pathology have been offered from a neurobiologic perspective (e.g., Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003). Broadly, these models posit an imbalance between neural circuits that govern reactive, automatic processes (often invoked by emotionally charged stimuli) versus goal-directed, context-driven processes, with the latter being selectively deficient, perhaps resulting in behaviour that is disproportionately or inappropriately driven by emotion. In this context, a recent review of SCZ neurocognition argues that

executing internally-generated, proactive control processes is a core dysfunction in SCZ that drives impairment across multiple cognitive domains, including context processing, working memory, and episodic memory (Barch & Ceaser, 2012). Importantly, populations characterized by deficient proactive control may exhibit increased reliance on reactive control processes (Barch & Ceaser, 2012).

Collectively, these models suggest that when emotional and contextual determinants of behaviour are put in conflict, context-dependent responding is diminished in SCZ and may be replaced by impulsive responding based on affectively salient aspects of the environment. It is important, therefore, to evaluate persons with SCZ using experimental tasks designed to index the resolution between competing emotional and contextual determinants of behaviour—the primary objective of the current investigation. The current study employed a novel paradigm, the context-emotion response task (CERT), which was designed to place emotional and contextual response cues in direct opposition.

The CERT was derived from previous research that characterizes our emotional behaviours as either approach (i.e., response to positive stimuli) or avoidance-related (i.e., response to negative stimuli). In this context, it has been shown that the emotional meaning of a stimulus can bias motor behaviour (Lewin, 1935). For example, Solarz (1960) found that making evaluative judgments on emotional stimuli, recorded by either pushing or pulling a lever, were faster for positively-judged stimuli during arm flexion (i.e., lever pulls) and faster for negatively-judged stimuli during arm extension (i.e., lever pushes). Cacioppo,

Priester, and Berntson (1993) subsequently developed the *motor-process hypothesis* (MPH) arguing that arm flexion is an approach-motivated action in response to appetitive stimuli, whereas arm extension is an avoidance-motivated action in response to aversive stimuli. An interesting body of research has since emerged, largely supporting the MPH (e.g., Cacioppo et al., 1993; Chen & Bargh, 1999; Cretenet & Dru, 2004; Maxwell & Davidson, 2007; Solarz, 1960). Cacioppo et al. (1993) observed that participants rated neutral stimuli more favourably when they were viewed in a static approach-motivated state (i.e., isometric arm flexion) than when viewed in a static withdrawal-motivated state (i.e., isometric arm extension), though subsequent research suggests that this effect may be moderated by the hand used (i.e., dominant or non-dominant; Cretenet et al., 2004) or by pre-existing attitudes about the neutral stimuli (Centerbar & Clore, 2006). In a subsequent experiment designed to remove the conscious evaluation of stimuli, Chen and Bargh (1999) observed that when participants were not required to rate a known stimulus as positive or negative, they still exhibited faster arm extension for negative stimuli and faster arm flexion for positive stimuli. Duckworth and colleagues replicated this finding using abstract stimuli that had been previously rated as either pleasant or unpleasant (Duckworth, Bargh, Garcia, & Chaiken, 2002). However, subsequent experiments have since suggested that conscious evaluation is central to the emergence of this motor effect (Rotteveel & Phaf, 2004). Nevertheless, each of these findings suggests that people have a prepotent motor response pattern to external stimuli that is modulated by judgments of emotional valence.

The CERT was developed with this prepotent response mapping in mind. In keeping with previous research, we predicted that judgments towards emotional pictures would be associated with an inherent motor bias – i.e., positive pictures would enhance arm flexion and negative pictures would enhance arm extension. Importantly, the CERT introduced an instructional cue on half of the trials that signaled a change in response mapping such that participants had to respond in opposition to this motor bias (i.e., extension to positive, flexion to negative). In doing so, we were able to examine the extent to which participants could inhibit emotion-driven motor responses when confronted with a contextual cue that impelled an alternative response. Thus, we were able to directly test the hypothesis that patients with SCZ would have greater difficulty than healthy individuals in using contextual cues to guide response selection when faced with competing emotional cues.

A secondary control task, the context-direction response task (CDRT), was used to determine if patients with SCZ had disproportionate difficulty overcoming emotional cues, or if they simply struggled with cue-conflict more generally. Rather than using emotional stimuli, the CDRT used neutral images that appeared to be either moving away from or moving towards the participant (i.e., zooming out or in). Participants were required to extend their arms for images that appeared to be moving away (i.e., incongruent condition) and flex their arms for images that appeared to be moving towards (i.e., congruent condition). As with the CERT, an instructional cue was used on certain trials that signaled a reversal of this response mapping. Therefore, a clear congruent/incongruent dichotomy was implemented

between the perceived trajectory of the moving picture and the subsequent arm movement. This conflict was created to be similar to the response mapping elicited by the emotional pictures in the CERT, less the emotional content. The CDRT provides an interesting empirical control as no studies to date have examined the resolution of emotional versus non-emotional response cue conflict in SCZ using separate tasks with analogous experimental parameters and task demands. It was hypothesized that individuals with SCZ would exhibit heightened difficulty with cue conflict on the CERT versus CDRT, thus reflecting a differential deficit in using contextual response cues to overcome emotional versus non-emotional response cues.

2.2 METHOD

2.2.1 Participants

The healthy control (HC) group ($n = 27$) ranged in age from 24 to 59 years and was recruited from online and community advertisements in the greater Hamilton, Ontario, Canada area (see Table 2.1 for sample characteristics). Inclusion criteria were: (a) ages 18 to 60 years; and, (b) normal or corrected-to-normal vision. Exclusion criteria were: (a) any self-reported history of brain damage, psychosurgery, loss of consciousness, and/or other diagnosable neurologic conditions; (b) a diagnosable psychiatric disorder as revealed by the Mini International Neuropsychiatric Interview (MINI; Sheehan, Lecrubier, Sheehan, Amorim, Janavs, et al., 1998); (c) a diagnosis of substance abuse within the past six months or lifetime substance dependence; (d) a first-degree relative with

schizophrenia-spectrum illness; (e) any psychotropic drug use during the fifteen days preceding their participation in the study; (f) reading ability below grade eight equivalent as assessed by the Wide Range Achievement Test 4th Edition (WRAT-4; Wilkinson & Robertson, 2006), and (g) self-reported colour blindness.

The SCZ group ($n = 27$) ranged in age from 27 to 56 years and was recruited from two outpatient clinics in the same community. Inclusion criteria for this group were that they: (a) met DSM-IV-TR criteria for Schizophrenia, Schizophreniform, or Schizoaffective disorder, as confirmed by a MINI and chart review⁶; (b) were aged 18 to 60 years; (c) had no change in medication status for at least 2 weeks; and (d) had normal or corrected-to-normal vision. Exclusion criteria were: (a) any self-reported history of brain damage, psychosurgery, loss of consciousness, and/or other diagnosable neurologic conditions; (b) a diagnosis of substance abuse within the past 6 months or lifetime substance dependence; (c) reading ability below grade eight equivalent, and (d) self-reported colour blindness. The Research Ethics Board at St. Joseph's Healthcare Hamilton approved this study in accordance with the provisions of the World Medical Association Declaration of Helsinki. All participants provided voluntary and informed consent and were provided compensation of \$10 per hour plus travel costs.

⁶ Patients did not differ on any of the parameters listed in Table 2.1 as a function of diagnostic category.

Table 2.1
Sample characteristics of HC and SCZ groups.

	HC	SCZ	<i>t</i> or χ^2	<i>p</i>
Age ^a	40.9 (9.4)	43.8 (8.0)	1.23	.22
Sex (<i>n</i> M/F)	13/14	25/2	12.79	< .01
Education ^a	15.3 (2.2)	13.3 (1.7)	3.74	< .01
Parental SES ^a	44.2 (15.6)	38.8 (7.5)	1.58	.12
Diagnosis (<i>n</i>)				
Schizophrenia	-	17	-	-
Schizoaffective	-	10	-	-
Medications (<i>n</i>)				
Typical antipsychotics	-	5	-	-
Atypical antipsychotics	-	23	-	-
Antidepressants	-	8	-	-
Anticonvulsants	-	8	-	-
Anticholinergics	-	2	-	-
Benzodiazepines	-	15	-	-
PANSS Positive ^a	-	40.9 (7.4)	-	-
PANSS Negative ^a	-	37.1 (6.2)	-	-
PANSS General ^a	-	35.2 (3.6)	-	-
PAI-Drug Problems ^a	48.9 (6.9)	56.3 (11.6)	2.85	.01
PAI-Alcohol Problems ^a	46.7 (3.4)	49.2 (11.9)	1.08	.29
WHODAS-II Total ^a	48.1 (5.9)	67.0 (12.1)	7.31	< .01
RBANS Total ^b	99.8 (14.8)	82.4 (13.0)	4.58	< .01
WAIS-III eFSIQ ^b	110.5 (13.4)	101.9 (14.1)	2.28	.03

Mean (SD); ^a*T* score; ^bStandard score; **eFSIQ** = Estimated Full-Scale intelligence quotient derived from the Matrix Reasoning and Information subtests of WAIS-III (Sattler & Ryan, 1998); **HC** = healthy control; **PAI** = Personality Assessment Inventory (Morey, 1990); **PANSS** = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); **SCZ** = schizophrenia; **SES** = Socioeconomic Status (Blishen, Carroll, & Moore, 1987); **WAIS-III** = Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997); **WHODAS-II** = World Health Organization Disability Assessment Schedule 2nd Edition (World Health Organization, 2000)

2.2.2 Baseline Assessment

All participants completed a baseline assessment to characterize their cognitive, clinical, and demographic status. Clinical characteristics and psychodiagnostic information was assessed using the MINI, Positive and Negative Syndrome Scale (PANSS—patients only; Kay, Fiszbein, & Opler, 1987), and an abbreviated version of the Personality Assessment Inventory (PAI; Morey, 1991). Baseline cognitive functioning was evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), an abbreviated form of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997), and the word reading subtest of the WRAT-4. In addition, information regarding basic demographics and functional status were collected using the World Health Organization Disability Assessment Schedule, 2nd Edition (WHODAS-II; World Health Organization, 2000). To minimize possible fatigue, the baseline assessment was done on a separate day prior to completing the experimental tasks.

2.2.3 CERT and CDRT

The CERT and CDRT used images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). The IAPS is a standardized set of pictorial stimuli comprised of emotionally positive, negative, and neutral images that have normative ratings on a 9-point scale for valence (1 = very unpleasant; 9 = very pleasant) and arousal (1 = low arousal; 9 = high arousal). Forty positive (valence: mean = 7.64, S.D. = 0.36; arousal: mean = 5.41, S.D. = 0.69), 40 negative images (valence: mean = 2.48, S.D. = 0.81; arousal: mean = 5.62, S.D. = 0.55) and 40

neutral images (valence: mean = 5.03, S.D. = 0.26; arousal: mean = 2.63, S.D. = 0.37) from the IAPS were used. IAPS arousal ratings for neutral images were significantly lower than both negative ($p < .001$) and positive ($p < .001$) images, whereas negative and positive images did not differ ($p = .09$). Valence ratings were different across each emotion category (all p -values $< .001$). Stimuli for both tasks were presented on a 19" LCD monitor situated 80 cm away from the participant. Responses were made on one of two buttons (6 cm in diameter) positioned radially from the participants' midline such that pressing button 1 (B1) required arm flexion and pressing the button 2 (B2) required arm extension. An additional button (home button) was located equidistant between B1 and B2 and served as the start position for each trial. Buttons were positioned 25 cm apart from one another (see Figure 2.1 for schematic of task apparatus).

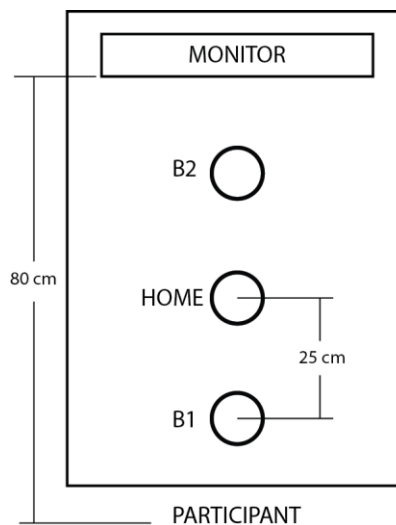


Figure 2.1 Schematic depiction of the experimental setup.

For the CERT, participants were shown a series of static negative and positive images in randomized order. Each image was paired with an instructional cue that preceded image presentation by 200 ms. On 50% of trials, a green border paired with a bell sound signaled participants to press B2 (extension) to negative images and press B1 (flexion) to positive images (i.e., congruent condition). On the other 50% of trials, a red border paired with a buzzer sound signaled participants to press B1 (flexion) to negative images and press B2 (extension) to positive images (i.e., incongruent condition). Auditory cues were heard only once per trial, whereas the coloured border remained for the duration of each trial. Congruent and incongruent instructional cues were also presented in randomized order. Stimuli remained on the screen for 10 seconds or until a response was made. The next trial was initiated by the participant depressing the home button after making their response, thus ensuring a uniform start position across trials and participants. If a response was not made within 10 seconds, the image would disappear and the screen would remain blank until the participant returned to the start position by pressing the home button, at which point the next trial would be initiated.

The presentation parameters and instructional cues for the CDRT were the same as the CERT. However, the stimuli consisted of neutral images that appeared to be moving towards or away from the participant. The green border/bell sound (i.e., congruent condition) signaled participants to press B2 (extension) to images that appeared to be moving away (MA) and press B1 (flexion) to images that appeared to be moving towards (MT). The red border/buzzer sound (i.e., incongruent condition)

signaled the opposite response mapping. The CERT and CDRT were administered in counterbalanced order across participants. Participants completed two practice blocks prior to both the CERT and CDRT, with each block consisting of only congruent or incongruent trials. These were included to ensure participants had adequately learned the response mapping demands across the various combinations of emotion/direction and instructional cue (Note: Mean accuracy on the CERT and CDRT practice blocks was $\geq 93\%$ for both groups). The order of practice blocks was counterbalanced to minimize the impact of potential reversal learning effects at a group level.

2.2.4 Data Preparation & Analysis

The dependent variables of interest for each task were average median response time (RT) in milliseconds and accuracy. Non-response trials (i.e., those trials in which participants did not respond before the image left the screen) and trials with RT less than 150ms were excluded from the statistical analysis⁷. Omnibus statistical analyses within each task consisted of a three-way repeated measures analysis of variance (ANOVA), with group (HC and SCZ) as the between-subjects factor and condition (congruent and incongruent) and valence (CERT; negative and positive) or direction (CDRT; MA and MT) as within-subject factors. The dependent variables of interest for each task were average median response time (RT) in

⁷ Mean (SD) number of non-response trials excluded on the CERT for the HC group was 0.48 (0.94) and the SCZ group was 0.48 (1.25). Mean (SD) number of non-response trials excluded on the CDRT for the HC group was 0.15 (0.60) and the SCZ group was 0.07 (0.27). Neither of these group differences were statistically significant ($ps > .1$). No trials had RT < 150ms in either group.

milliseconds and accuracy. Simple main effect testing was performed via paired-sample *t*-tests using Bonferroni-corrected alpha values. Planned between-task comparisons were then carried out within each group to examine the hypothesized between-task difference in the SCZ group—i.e., greater difficulty overcoming cue conflict on the CERT versus CDRT. The difference between congruent and incongruent trials (collapsed across valence and direction) was calculated for both RT and accuracy and these served as dependent variables. Larger difference scores were indicative of worse performance on incongruent trials (slower RT or lower accuracy). Finally, to better characterize associations between task performance and clinical variables, bivariate correlational analyses were performed between accuracy and RT difference scores and measures of psychopathology (PANSS and PAI) and neuropsychological functioning (RBANS and IQ) within the SCZ group. Correlation analysis used a more conservative alpha value of .01 to account for multiple comparisons and minimize the possibility of Type I error. Effect sizes are reported as partial eta squared (η_p^2) and Cohen's *d*. Raw RT and accuracy data are summarized in Table 2.2.

2.2.5 Accounting for Task Difficulty

An important caveat associated with investigating differential ability in psychopathology research is a potential difficulty confound (see Chapman & Chapman, 1978). Briefly, if two tasks are matched on all parameters except item content (as with the CERT and CDRT), yet they differ psychometrically in terms of overall difficulty in a control sample, inferences about differential ability on one task

versus the other in a clinical sample may be misleading. For example, it is possible that a performance decrement observed on the CERT versus CDRT in the SCZ group might result from incongruent trials being inherently more difficult than congruent trials on the CERT. To examine this possibility, we used RT and accuracy data from the HC group to compute drift rate (v)⁸. Drift rate is an EZ diffusion model parameter that combines RT variance and accuracy into one variable that quantifies signal-to-noise ratio and, by extension, task difficulty (Wagenmakers, van der Maas, & Grasman, 2007). Drift rate was computed for congruent and incongruent trials in both tasks and used as the dependent variable in a condition x task repeated-measures ANOVA. If incongruent trials were disproportionately more difficult than congruent trials on the CERT, we would expect to see a task x condition interaction. If no such interaction is observed, then we could reasonably argue that any potential CERT-CDRT difference within the SCZ group was not a spurious effect brought on by a difficulty confound.

⁸ RT and accuracy data were fit to the EZ diffusion model to obtain drift rate (Wagenmakers et al., 2007). In the EZ diffusion model, decision-making on a two-alternative choice task is conceptualized as the “gradual accumulation of noisy information” until a specific threshold for one choice is reached (p. 149; Wagenmakers, Krypotos, Criss, & Iverson, 2012). Therefore, higher drift rate values signify a larger signal-to-noise ratio and, by extension, lower task difficulty. For the current study, the two choices would be represented by button 1 and button 2, with signal being provided by picture emotion/direction and instructional cue. A more detailed description of the mathematical derivation and applications of the EZ diffusion model can be found in Wagenmakers et al. (2007, 2012).

Table 2.2 Average median RT (ms) and accuracy as a function of group, task, and condition.

	Healthy Control		Schizophrenia	
	Response Time	Accuracy	Response Time	Accuracy
Emotion task				
NEG CON	1901 (448)	0.93 (0.15)	2336 (554)	0.89 (0.12)
POS CON	1658 (416)	0.96 (0.09)	1954 (491)	0.96 (0.11)
NEG INCON	2005 (492)	0.92 (0.09)	2522 (631)	0.88 (0.16)
POS INCON	2048 (498)	0.89 (0.14)	2507 (681)	0.88 (0.15)
Direction task				
MA CON	1686 (452)	0.98 (0.05)	2205 (767)	0.91 (0.12)
MT CON	1540 (242)	0.98 (0.05)	1924 (766)	0.94 (0.10)
MA INCON	1854 (486)	0.93 (0.14)	2294 (798)	0.85 (0.19)
MT INCON	1721 (440)	0.96 (0.09)	2245 (786)	0.83 (0.19)

Mean (S.D.); Abbreviations: CON = Congruent; INCON = Incongruent; MA = Moving Away; MT = Moving Towards; NEG = Negative; POS = Positive

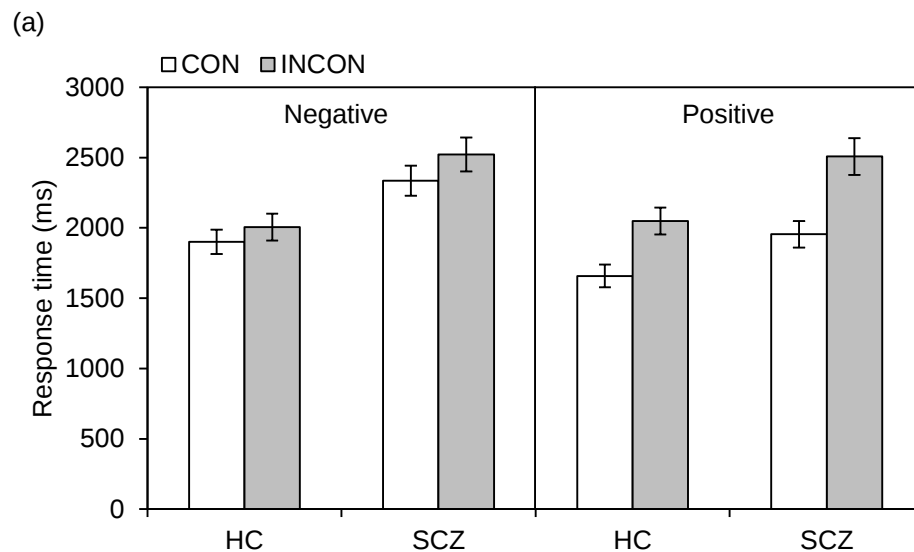
2.3 RESULTS

2.3.1 Context-Emotion Response Task (CERT)

RT and accuracy data were not significantly correlated within either group, indicating that speed-accuracy trade-off was not a factor on this task. For RT data, main effects of condition, $F(1,52) = 34.25$, $p < .001$, $\eta_p^2 = 0.40$, and valence, $F(1,52) = 8.06$, $p = .006$, $\eta_p^2 = 0.13$, were observed, reflecting slower RT on incongruent and negative trials, respectively. The main effect of condition provides some measure of validation for the emotion-driven response mapping outlined in the motor process hypothesis (i.e., faster flexion to positive and extension to negative stimuli). The condition and valence main effects, however, must be qualified with the observed condition x valence interaction, $F(1,52) = 13.05$, $p = .001$, $\eta_p^2 = 0.20$ (see Figure

2.2a). Decomposition of this interaction showed the simple main effect of valence (negative slower than positive) was only significant on congruent trials, $t(53) = 5.06$, $p < .001$, $d = 0.61$. A main effect of group was also observed, $F(1,52) = 13.49$, $p = .001$, $\eta_p^2 = 0.21$, reflecting slower RTs in the SCZ group.

For accuracy data, a main effect of condition was observed, $F(1,52) = 7.28$, $p = .009$, $\eta_p^2 = 0.12$, reflecting lower accuracy on incongruent trials. This reinforces the aforementioned validation of the motor-process hypothesis provided by the RT data. However, the condition effect must be interpreted within the context of a condition x valence interaction that was significant at trend levels, $F(1,52) = 3.67$, $p = .06$, $\eta_p^2 = 0.07$. Decomposition of this interaction showed that the simple main effect of condition was only significant for positive images, $t(53) = 3.56$, $p = .001$, $d = 0.58$ (see Figure 2.2b), and the simple main effect of valence (i.e., negative less accurate than positive) was only significant for congruent trials, $t(53) = 2.41$, $p = .02$, $d = 0.41$. No main or interaction effects involving group were observed.



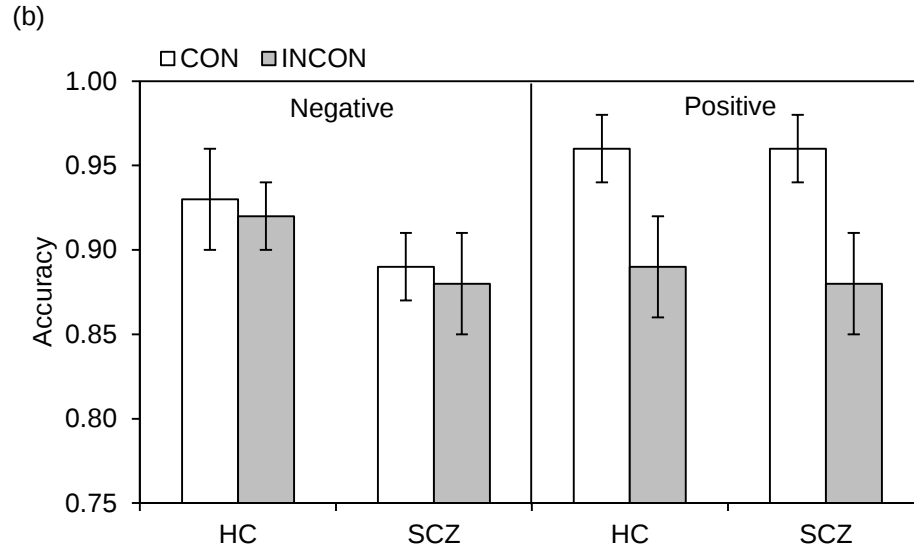


Figure 2.2 Graphical depiction of (a) RT and (b) accuracy data on the CERT as a function of group, valence and condition.

2.3.2 Context-Direction Response Task (CDRT)

As with the CERT, RT and accuracy data were not significantly correlated within either group, indicating that speed-accuracy trade-off was not a factor on this task. For RT data, main effects of condition, $F(1,52) = 25.85, p < .001, \eta_p^2 = 0.33$, and direction, $F(1,52) = 19.54, p < .001, \eta_p^2 = 0.27$ were observed, reflecting slower RT on incongruent and MA trials, respectively (see Figure 2.3a). A main effect of group was also observed, $F(1,52) = 9.06, p = .004, \eta_p^2 = 0.15$, reflecting slower RT in the SCZ group. No significant interaction effects were observed. For accuracy data, main effects of condition, $F(1,52) = 15.72, p < .001, \eta_p^2 = 0.23$, and group, $F(1,52) = 9.09, p = .004, \eta_p^2 = 0.15$, were observed, reflecting lower accuracy on incongruent trials and in the SCZ group, respectively (see Figure 2.3b). The condition effects

observed for both RT and accuracy data are notable as they indicate that the CDRT elicited an incongruency effect that was qualitatively similar to the CERT.

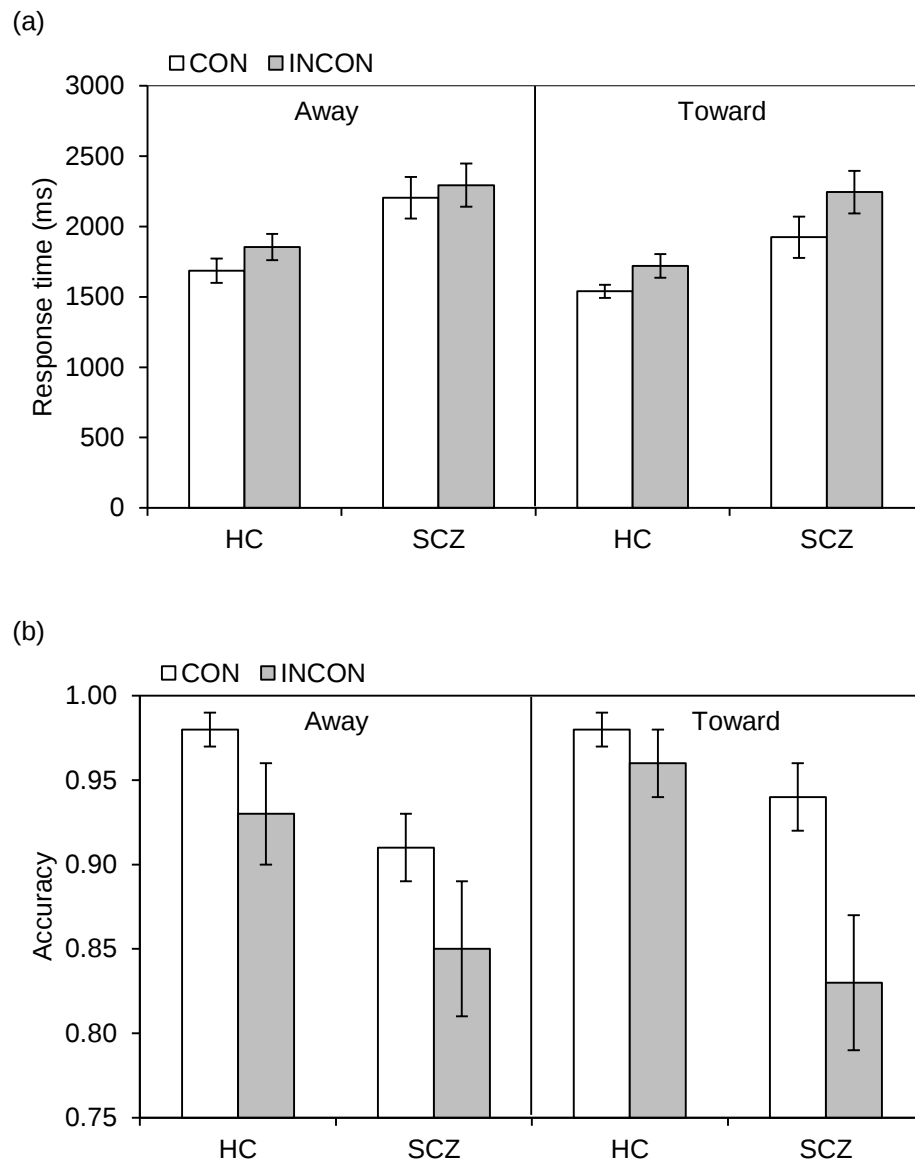


Figure 2.3 Graphical depiction of (a) RT and (b) accuracy data on the CDRT as a function of group, direction and condition.

2.3.3 Planned Comparison of CERT versus CDRT

The HC group did not exhibit differential performance across tasks for RT difference scores (incongruent – congruent) or accuracy difference scores (congruent – incongruent) ($ps > .10$). By contrast, RT difference scores in the SCZ group were over 160ms greater on the CERT versus CDRT, $t(26) = 1.75$, $p = .04$, $d = 0.42$ (one-tailed). Accuracy difference scores did not differ across tasks in the SCZ group ($p > .10$). These data indicate the SCZ group had greater response slowing on incongruent trials within the CERT relative to the CDRT, whereas the HC group demonstrated statistically non-significant differences across tasks for accuracy, $t(26) = 1.12$, $p = .27$, $d = 0.27$, and RT, $t(26) = 0.13$, $p = .90$, $d = 0.04$ (see Figure 2.4). Bivariate correlation analysis within the SCZ group showed significant negative correlations between CDRT RT difference scores and RBANS Immediate Memory Index ($r = -.76$, $p < .01$) and RBANS Total Index ($r = -.57$, $p < .01$).

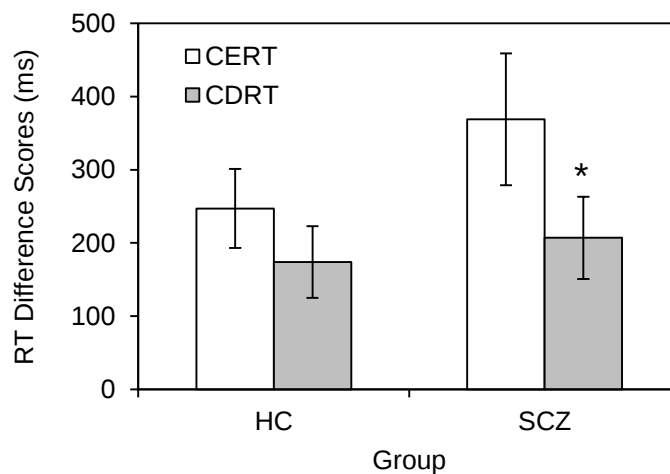


Figure 2.4 Graphical depiction of RT difference scores as a function of group and task. Difference scores were computed by subtracting RT in the congruent condition from RT in the incongruent condition. * $p = .04$ (one-tailed).

2.3.4 Task Difficulty Analysis

In this HC group, only main effects of condition, $F(1,26) = 32.93, p < .001, \eta_p^2 = 0.56$ (congruent > incongruent), and task, $F(1,26) = 21.91, p < .001, \eta_p^2 = 0.46$ (CDRT > CERT), were observed, whereas the condition x task interaction was not significant, $F(1,26) = 0.34, p = .56, \eta_p^2 = 0.01$. Although the main effect of task indicates the CERT was generally more difficult than the CDRT, the magnitude of difference between congruent and incongruent trials was equivalent across tasks (i.e., no condition x task interaction). This suggests that the difference scores that were used to make between-task comparisons were not differentially affected by variability in overall task difficulty. Consequently, the disproportionate difficulty on incongruent trials of the CERT versus CDRT observed in the SCZ group was likely not a difficulty artifact.

2.3.5 Exploratory Subgroup Analysis

It has recently been suggested that different aspects of SCZ symptomatology are associated with distinct conflict resolution deficits. Kerns (2009) argues that resolving response conflict—i.e., when habitual or prepotent responding must be inhibited by executive control processes—is associated with disorganized symptoms. Given that emotion-laden stimuli often invoke automatic, prepotent responses (MacDonald, 2008), it stands to reason that incongruent trials on the CERT would elicit a disproportionately large response conflict relative to the CDRT. With this in mind, an exploratory analysis was performed in which the SCZ group was subdivided into patients who exhibited disorganized symptoms ($n = 15$) and those

who did not ($n = 12$; see Appendix A for sample characteristics). Patients were characterized as having disorganized symptoms if they scored in the mild to severe range on PANSS conceptual disorganization, mannerisms and posturing, and/or distorted thought content. Consistent with Kerns (2009), patients with disorganized symptoms showed larger RT difference scores on the CERT versus CDRT, $t(14) = 2.33$, $p = .035$, $d = 0.74$, whereas non-disorganized patients did not show differential performance across tasks for either RT or accuracy difference scores (both $ps > .10$).

2.4. DISCUSSION

The current study investigated how individuals with SCZ reconcile competing emotional and contextual response determinants. The CERT employed instructional cues that required a response either consistent with (congruent), or in opposition to (incongruent), emotion-driven, prepotent motor actions. The CDRT was created in order to evaluate qualitatively similar response conflicts outside of an emotional context. In particular, we sought to examine whether patients with SCZ would exhibit *selective* difficulty in overcoming emotional cues, or if they would demonstrate deficits in cue-conflict management more generally. We hypothesized that individuals with SCZ would demonstrate disproportionate difficulty on incongruent trials within the CERT relative to the HC group. We further hypothesized that the SCZ group would have more difficulty overcoming cue-conflict on the CERT versus CDRT.

On the CERT, the SCZ group was generally slower and less accurate than HCs. In addition, both groups were slower to respond on incongruent versus congruent trials, regardless of emotional valence. The main effect of condition is important as it provides further validation of the MPH (i.e., enhanced flexion and extension for positive and negative images, respectively). Interestingly, both groups were slower and less accurate in responding to negative images on congruent trials. Response slowing to negative images may be reflective of a broader defensive reaction when confronted with threatening or aversive stimuli. Azevedo and colleagues (2005) observed an increase in postural immobility and rigidity, as well as pronounced bradycardia in healthy males when viewing unpleasant images. This “freezing-like posture” was interpreted as the activation of a defensive system “mediated by neural circuits that promote survival” (p.255, Azevedo et al., 2005). Given that both groups in the current study exhibited similar response slowing to negative images, this automatic response may be intact in patients with SCZ. However, it remains unclear why accuracy was also reduced for negative images and why this general valence effect only occurred on congruent trials.

Contrary to the first hypothesis, SCZ patients did not show a disproportionate deficit in RT or accuracy on incongruent trials of the CERT compared to HCs. Although mean RT on incongruent trials was, on average, over 120 ms slower in the SCZ group, the group by condition interaction was not significant ($p > .10$). This suggests SCZ and HC participants were statistically equivalent in terms of their ability to use contextual response cues in order to overcome prepotent, emotion-

driven behaviour on this task. This finding runs counter to behavioural predictions derived from psychological and neurobiologic models of SCZ (Christensen & Bilder, 2000; Grace, 2003; Giaccio, 2006; Speechley & Ngan, 2008). Moreover, these data are inconsistent with a recent study that was anchored in the same broad theoretical framework (Patrick & Christensen, 2013). Using an emotional directed-forgetting (DF) paradigm, Patrick and Christensen (2013) observed that SCZ patients were less able to forget negative words when instructed to do so by a forget cue. The authors suggested that this may have reflected a deficit in patients' ability to deploy inhibitory mechanisms (elicited by the forget cue) in order to override an opposing, prepotent emotional response—the automatic memory enhancement of emotional material.

The disparity in findings between the CERT and the emotional DF task may be explained by both theoretical and methodological considerations. First, although observed power on the CERT was adequate to detect main effects of condition, valence, and group, as well as the condition by valence interaction (all ≥ 0.80), observed power for the group by condition interaction term was substantially lower (0.21). This suggests that, within this particular task, the interaction of the experimental manipulation with group is small and may have achieved statistical significance with a larger sample size. Second, the current study required participants to consciously evaluate the emotional valence of stimuli, whereas the emotional DF paradigm used by Patrick and Christensen (2013) did not. Previous research suggests that conscious evaluation increases the strength of prepotent, emotion-driven responses. For example, Chen and Bargh (1999) observed that the congruency effect

(i.e., enhanced flexion and extension for pleasant and unpleasant stimuli, respectively) was larger when healthy volunteers had to consciously (Cohen's d effect size = 0.56) versus unconsciously ($d = 0.39$) evaluate stimuli for pleasantness. The current study's requirement for overt emotional judgments might have made it more difficult for *all* participants to override their emotional motor responses, not just patients with SCZ. If so, obtaining a statistically significant group by condition interaction would have required severely impaired performance on incongruent trials in the SCZ group. Although the group by condition interaction was in the predicted direction, the magnitude of this effect was not large enough to reach statistical significance. Future studies could offer some clarity in this regard by comparing congruency effects across tasks which differ in the extent to which emotional stimuli must be consciously evaluated.

On the CDRT, the SCZ group was generally slower and less accurate than HCs. In addition, both groups were slower to respond on incongruent versus congruent trials, regardless of direction. The main effect of condition is important as it suggests the CDRT was a reasonable non-emotional analog of the CERT in terms of congruency-incongruency effects. This notion is bolstered by the observed similarities in difficulty (as indexed by drift rate) between congruent and incongruent trials for both tasks. Interestingly, participants in both groups exhibited faster response times for MT images, regardless of condition. This direction effect may reflect an evolved, visual perceptual mechanism used to compute time-to-collision (TTC). Frost and Sun (2003) note that "the sight of a rapidly approaching object

almost universally signals danger” in the animal kingdom and forces the visual system to “compute the TTC of the object to provide the information necessary for eliciting and controlling appropriate evasive action” (p. 15). Single cell recording experiments in both pigeons (Sun & Frost, 1998) and locusts (Hatsopoulos, Gabbiani, & Laurent, 1995) have detected neurons that respond optimally to approaching objects that are on a direct collision course. Therefore, it is plausible that all participants, regardless of group, were faster to respond to MT images because these stimuli elicited an evolved defensive reaction in response to objects that appeared to signal an impending collision.

Consistent with the second hypothesis, the SCZ group demonstrated a greater incongruency effect on the CERT relative to the CDRT (as indexed by RT differences scores), whereas the HC group showed equivalent performance across tasks. These findings offer tentative evidence that patients with SCZ have greater difficulty inhibiting emotional versus non-emotional response cues when task demands call for such action. This observation, however, should be interpreted with some degree of caution as the HC group demonstrated a qualitatively similar pattern across tasks, albeit at reduced magnitude. Interestingly, when patients were subdivided according to the presence or absence of disorganized symptoms, the larger incongruency effect was only observed in patients with disorganized symptoms. This suggests that disproportionate difficulty in overcoming emotional versus non-emotional response cues might be unique to patients for whom disorganized symptoms are a prominent part of their clinical presentation. This

finding is consistent with Kerns' (2009) conceptualization of symptom-specific conflict resolution deficits in SCZ, namely the association between disorganized symptoms and prepotent response conflict. Future experiments that investigate emotion-context response conflict would likely benefit from a finer-grained, *a priori* examination of how different aspects of SCZ symptomatology contribute to difficulties in resolving this conflict. More generally, our results highlight the utility of characterizing psychiatric samples according to relevant dimensions of psychopathology, as opposed to using circumscribed diagnostic categories that largely fail to account for prominent intra-group heterogeneity.

An important methodological consideration that warrants further discussion concerns the task-switching element invoked by the CERT and CDRT. Recent research suggests that task-switching deficits in SCZ are strongest on tasks that place high demands on contextual processing (e.g., Ravizza, Keur Moua, Long, & Carter, 2010). In the current study, the trial-to-trial variability in response mapping introduced by changing contextual cues was an important shared characteristic of both tasks. Therefore, it is possible that the observed pattern of data simply reflected a general context-dependent task-switching deficit in SCZ, rather than selective difficulty in overriding emotional (versus non-emotional) response cues. Indeed, the main effect of group observed on *both* tasks would seem to support such an argument. That said, although a general task-switching deficit may have contributed to the between-group variance, the between-task difference observed within the SCZ group

cannot be accounted for by task-switching demands. Instead, the CERT appears to have been inherently more challenging for SCZ patients.

An important limitation of the current study concerns the sex ratio across groups, namely the large male-to-female ratio in the patient group only. Having an unequal sex ratio is potentially problematic given documented sex differences in emotion-cognition interactions. For example, Koch et al. (2007) observed that, in women, the interaction between negative emotion induction and working memory was associated with relative hyperactivation in regions associated with emotional processing, such as the amygdala and orbitofrontal cortex. This suggests that women may have a “biologically grounded greater sensitivity and vulnerability to adverse/stressful events” (p. 925, Bianchin & Angrilli, 2012). Therefore, the relative lack of female SCZ patients in the current study may have resulted in smaller group-level emotional reactivity, thereby diminishing the strength of emotion-cognition antagonism invoked by the CERT.

2.5 SUMMARY & CONCLUSIONS

In summary, the present investigation demonstrated that individuals with SCZ did *not* differ significantly from HC in terms of their ability to utilize contextual response cues in the face of countermanding emotional response cues. However, the SCZ group’s ability to use contextual cues to inhibit emotion-driven responding was worse relative to non-emotional responding. This tentatively supports the notion that patients with SCZ have disproportionate difficulty disengaging from *emotion*-driven thought and behaviour when task demands or situational context call for such re-

direction, though future studies would benefit from a more detailed analysis of how different dimensions of SCZ psychopathology contribute to resolving this conflict using larger samples. Collectively, these data add to a growing body of literature concerning the nature of abnormal emotion-cognition interactions in SCZ. Moreover, the current study offers partial support for recent neurobiologic and psychological models of SCZ pathology which predict diminished influence of contextual response cues when faced with competing emotional response cues. It would be advantageous for future studies to investigate such emotion-cognition interactions using direct neurobiologic assays. Task-dependent neuroimaging techniques that examine temporal and structural patterns of functional connectivity among dorsal and ventral trend structures, such as those outline by Giaccio (2006) and Christensen and Bilder (2000), would be particularly informative in this regard.

Appendix A

Sample characteristics of disorganized and non-disorganized patient groups.

	Non-disorganized	Disorganized	<i>t</i> or χ^2	<i>p</i>
Age ^a	42.42 (8.58)	44.93 (7.70)	0.80	.43
Sex (<i>n</i> M/F)	10/2	15/0	2.70	.10
Education ^a	13.58 (2.07)	13.00 (1.41)	0.87	.39
SES ^a	39.09 (9.59)	38.63 (5.48)	0.14	.88
Diagnosis (<i>n</i> SZ/SA/SP)	7/5/0	10/5/0	0.20	.66
PANSS Positive ^a	36.67 (5.21)	44.20 (7.35)	2.99	< .01
PANSS Negative ^a	38.17 (7.37)	36.20 (5.09)	0.82	.42
PANSS General ^a	35.58 (4.21)	34.87 (3.04)	0.51	.61
PAI-Drug Problems ^a	51.83 (8.58)	59.87 (12.65)	1.88	.07
PAI-Alcohol Problems ^a	50.42 (7.53)	48.27 (14.67)	0.46	.65
WHODAS-II Total ^a	66.42 (14.47)	67.53 (10.34)	0.23	.82
RBANS Imm. Memory ^b	83.17 (13.33)	73.40 (11.26)	2.06	.05
RBANS Visuospatial ^b	99.75 (22.54)	96.00 (18.01)	0.48	.64
RBANS Language ^b	93.92 (9.24)	88.47 (11.70)	1.32	.20
RBANS Attention ^b	83.92 (17.63)	85.60 (17.89)	0.24	.81
RBANS Delayed Memory ^b	87.17 (20.99)	77.00 (15.15)	1.46	.16
RBANS Total ^b	86.25 (14.80)	79.27 (10.93)	1.41	.17
WAIS-III eFSIQ ^b	106.83 (17.13)	98.00 (10.01)	1.68	.11

Note: Mean (SD); ^a*T* score; ^bStandard score; **Abbreviations:** eFSIQ = Estimated Full-Scale intelligence quotient derived from the Matrix Reasoning and Information subtests of WAIS-III (Sattler & Ryan, 1998); PAI = Personality Assessment Inventory (Morey, 1990); PANSS = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); RBANS = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); SZ = Schizophrenia; SA = Schizoaffective; SP = Schizophreniform; SES = Socioeconomic Status (Blishen, Carroll, & Moore, 1987); WAIS-III = Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997); WHODAS-II = World Health Organization Disability Assessment Schedule 2nd Edition (World Health Organization, 2000).

ACKNOWLEDGMENTS

This research was supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research awarded to Regan Patrick. The authors would like to thank Iulia Patriciu, Katie Herdman, and Carolyn Roy for their contributions towards participant recruitment, data collection, and data management. The authors would also like to thank John Potwarka for his assistance in programming the experiments.

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CHAPTER 3

EFFORTFUL VERSUS AUTOMATIC EMOTIONAL PROCESSING IN SCHIZOPHRENIA: INSIGHTS FROM A FACE- VIGNETTE TASK

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ABSTRACT

Adaptive emotional responding relies on dual automatic and effortful processing systems. Dual-stream models of schizophrenia (SCZ) posit a selective deficit in neural circuits that govern goal-directed, effortful processes versus reactive, automatic processes. This imbalance suggests that when patients are confronted with competing automatic and effortful emotional response cues, they will exhibit diminished effortful, goal-directed responding and intact, possibly elevated, automatic responding compared to controls. This prediction was evaluated using a modified version of the face-vignette task (FVT). Participants viewed emotional faces (automatic response cue) paired with situational vignettes (effortful response cue) that signaled a different emotion category and were instructed to discriminate the manifest emotion. Patients made less vignette and more face responses than controls. However, the relationship between group and FVT responding was moderated by IQ and reading comprehension ability. These results replicate and extend previous research and provide tentative support for abnormal conflict resolution between automatic and effortful emotional processing predicted by dual-stream models of SCZ.

3.1 INTRODUCTION

Adaptive emotional responding relies on both automatic and effortful processing streams (e.g., MacDonald, 2008; Phillips, Drevets, Rauch, & Lane, 2003). The automatic processing stream is evolutionarily older and recruited in response to motivationally or biologically significant stimuli in one's environment (MacDonald, 2008). This might include, for example, a disgust response when confronted with a known contaminant (Tybur, Lieberman, Kurzban, & DeScioli, 2013) or the rapid appraisal of threatening facial expressions (Ohman, 2009). Such reactive responses, however, are not completely invariant. The effortful processing stream can provide top-down, goal-directed reappraisal of emotion-laden stimuli in order to contextually regulate affect-driven responding (MacDonald, 2008; Phillips et al., 2003). Ochsner and Gross (2005) call this process "controlled regulation" and suggest that it facilitates the reinterpretation of a stimulus in order to alter one's emotional response (p. 245). In this way, emotional behaviour can be enacted in a manner consistent with one's situational or behavioural context.

Research suggests that automatic emotional processing is relatively preserved in schizophrenia (SCZ; Hoschel & Irle, 2001; Schwartz, Vaidya, Howard, & Deutsch, 2010). For example, patients often do not differ from healthy controls (HC) in their immediate subjective reactions (i.e., valence and arousal ratings) to emotionally evocative stimuli in laboratory studies (Herbener et al., 2008; Llerena, Strauss, & Cohen, 2012). Similarly, emotion-modulated physiologic responses, such as electrodermal skin response and startle eyeblink, are generally intact among

patients (Kring & Moran, 2008). Early-stage event-related potentials (ERPs) in response to emotional stimuli are also largely unaffected in SCZ. For example, Horan and colleagues (2012) have shown that the Early Posterior Negativity (EPN), which indexes early and relatively automatic attentional engagement, does not differ between patients and controls when viewing emotional versus neutral pictures (Horan, Foti, Hajcak, Wynn, & Green, 2012). Comparable results have been obtained for other components reflective of early electrocortical processing, including P1, P2, and P3 (Horan, Wynn, Kring, Simons, & Green, 2010). Of note, a recent meta-analysis suggests that patients may experience elevated subjective aversion in response to neutral and pleasant stimuli (Cohen & Minor, 2010; Llerena et al., 2012), perhaps reflecting untempered or unregulated automatic negative emotionality.

In this context, there is some evidence to suggest that effortful, goal-directed emotional processing is diminished in SCZ (Roux, Christophe, & Passerieux, 2010; van't Wout, Aleman, Kessels, Cahn, de Haan, & Kahn, 2007). For example, patients report less use of perspective taking (i.e., reappraisal) when self-regulating negative affect (Rowland et al., 2013; van der Meer, van't Wout, & Aleman, 2009). Similarly, abnormal emotion-regulation, namely impulse control, has been found to be associated with persecutory ideation in a sub-clinical sample (Westermann & Lincoln, 2011). Patients with SCZ also show relatively impaired explicit versus implicit processing of facial emotion (Linden et al., 2009) and prosody (Roux et al., 2010). At a neural level, psychosis prone individuals exhibit reduced functional connectivity between prefrontal cortex and amygdala when instructed to cognitively

reappraise negative images (Modinos, Ormel, & Aleman, 2010). Patients with SCZ also show diminished alteration of ERP responses (i.e., late positive potential) to unpleasant images after being instructed to pre-appraise them in a more neutral light (Horan, Hajcak, Wynn, & Green, 2013; Strauss, Kappenman, Culbreth, Catalano, Lee, & Gold, 2013), which was interpreted as an impairment in controlled regulation of emotional responding.

To date, little research has explored how patients reconcile conflict between competing response cues that impel automatic versus effortful emotional processing—the primary objective of the current study. This is an important target of investigation in light of neural models of SCZ that posit an imbalance between circuits that govern reactive, automatic processes versus goal-directed, effortful processes (Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003; Phillips et al., 2003). Briefly, Phillips et al. (2003) have outlined distinct ventral and dorsal systems corresponding to automatic and effortful/voluntary emotional processing streams, respectively. The ventral system—comprised of the amygdala, insula, ventral striatum, and ventral anterior cingulate cortex (ACC)—is responsible for the initial rapid appraisal and identification of emotional stimuli, as well as autonomic response regulation. By contrast, the dorsal system—consisting of the hippocampus, dorsal ACC, and dorsolateral prefrontal cortex (PFC)—is implicated in the volitional regulation and top-down modulation of affective states and emotional behaviours. In this context, several neurobiological models have argued that SCZ is characterized by selective deficiencies within dorsal neural systems (Christensen & Bilder, 2000;

Giaccio, 2006). This assertion is supported by a substantial body of research implicating neurologic and functional abnormalities in SCZ that selectively involve regions within the dorsal system, including the hippocampal formation, dorsal ACC, dorsolateral PFC, and dorsal visual stream (Barch & Ceaser, 2012; Butler et al., 2001; Elahipanah, Christensen & Reingold, 2011; Giaccio, 2006; King, Christensen & Westwood, 2008). By contrast, there is evidence for relative sparing of ventral system structure (Chance, Esiri, & Crow, 2002; Selemon, Mrzljak, Kleinman, Herman, & Goldman-Rakic, 2003) and function (Danion, Meulemans, Kauffmann-Muller, & Vermaat, 2001; Demily et al., 2010; King et al., 2008). In the context of emotional processing, a dorsal system deficiency predicts that when SCZ patients are confronted with a situation that pits automatic and effortful emotional processes in direct conflict, they will exhibit diminished effortful responding (i.e., emotional responses that require deliberate, controlled processing), perhaps leading to elevated, automatic responding compared to HCs. This prediction, however, has not been tested in a clinical sample.

Competition between effortful and automatic emotional processing was examined in the current study using the face-vignette task (FVT; Carroll & Russell, 1996; Green et al., 2007). The FVT requires participants to read a short situational vignette and then view an emotional face representing the hypothetical person described in the vignette. Participants are then asked to indicate what emotion the person is feeling (in multiple-choice format) based on all available information. Importantly, the emotions depicted by the face and vignette are discordant, thereby

necessitating that participants base their responses on either the information provided by the vignette or the face. This paradigm is well-suited for the current study's objectives as the emotional stimuli—faces and vignettes—embody the automatic versus effortful dichotomy described above. Faces capture attention more readily than other objects in one's environment (Ro, Russell, & Lavie, 2001) and information from emotional facial expressions is extracted even more rapidly and automatically (for detailed reviews, see Straube, Mothes-Lasch, & Miltner, 2011; Vuilleumier, 2002). Indeed, Vuilleumier (2002) concludes there is “remarkable convergence of behavioural and neurophysiological evidence suggesting that our brain is equipped with mechanisms for enhancing the detection of and reaction to emotional facial information” (p. 297). For example, electrophysiological studies have found that very early latency ERP waveforms (i.e., within 170ms) can reliably discriminate emotional and neutral facial expressions (Smith, 2012). Processing emotional faces is thought to occur without conscious awareness because we are “evolutionarily prepared to respond” to such stimuli via a dedicated subcortical pathway to the amygdala (p. 704; Tamietto & de Gelder, 2010). It is highly unlikely that a similar level of automaticity has evolved for extracting emotional information from written prose given the cultural specificity of this type of stimuli. On the contrary, ascertaining the emotional meaning of a character-based written narrative likely necessitates several higher-level processes, such as theory of mind, sensitivity to story structure, inference making, and comprehension monitoring (Altmann, Bohrn, Lubrich, Menninghaus, & Jacobs, 2012; Randi, Newman, & Grigorengko, 2011).

Therefore, by examining the pattern of face and vignette-based responses across groups on the FVT, one can determine the extent to which SCZ patients' behavioural output is reflective of automatic versus effortful, goal-directed emotional processing.

The only previous study to use the FVT in a SCZ sample found that, relative to HCs, patients made less vignette-based responses, were equivalent in face-based responses, and made more random responses (i.e., chose an emotion that was not depicted by either the face or vignette; Green et al., 2007). The authors interpreted these findings as a deficit in emotional context processing, which we argue is akin to the controlled, effortful processes described above as it requires a situationally-based reappraisal of more automatically processed facial emotion information. However, there are important methodological considerations that warrant the need for replication. First, vignettes and faces were presented sequentially, with vignettes always shown first. In doing so, participants had to maintain details of the vignette in mind while viewing only the facial stimuli prior to making a response. This likely placed significant demands on working memory, a well-documented cognitive deficit in SCZ (e.g., Forbes, Carrick, McIntosh, & Lawrie, 2008). Therefore, the reduced number of vignette-based responses in the SCZ group may have reflected a disruption in working memory, rather than differential use of vignette versus facial information. Second, variance attributable to reading comprehension ability was not explored. This is critical as the validity of conclusions drawn from this type of paradigm hinges on the participants' capacity to read and understand the written information provided by the vignettes. In addition, recent investigations of reading comprehension in SCZ

have found impairments in sentence and paragraph comprehension (Arnott, Sali, & Copeland, 2011; Hayes & O'Grady, 2003). Moreover, Bagner and colleagues reported a link between working memory deficits and reading comprehension in SCZ (Bagner, Melinder, & Barch, 2003), further highlighting the importance of accounting for both of these factors via empirical and statistical methods. Third, it is important to account for variance attributable to basic emotional face processing. As with reading comprehension, the validity of interpretations drawn from this type of paradigm depends on the extent to which participants' can accurately identify facial emotions in isolation (Green et al., 2007). This is particularly important in light of well-documented deficits in facial emotion processing in SCZ (Morris, Weickert, & Loughland, 2009). Given these considerations, several experimental and statistical modifications were made in order to better account for the influence of working memory, reading comprehension ability, and basic facial emotion processing (detailed in Methods), thereby providing a richer explanation of FVT response abnormalities among SCZ patients. We hypothesized that SCZ patients would make less vignette-based and more face-based responses relative to HCs, reflecting diminished effortful, goal-directed emotional processing in the face of competing stimuli that impel an opposing, more automatic emotional response.

3.2 METHOD

3.2.1 Participants

The HC group ($n = 29$) ranged in age from 24 to 59 years and was recruited from online and community advertisements in the greater Hamilton, Ontario,

Canada area (see Table 3.1 for sample characteristics). Inclusion criteria for this group were: (a) aged 18 to 60 years old; and, (b) normal or corrected-to-normal vision. Exclusion criteria were: (a) any self-reported history of brain damage, psychosurgery, or loss of consciousness, and/or other diagnosable neurologic conditions; (b) a diagnosable psychiatric disorder as revealed by the Mini International Neuropsychiatric Interview (MINI; Sheehan, Lecrubier, Sheehan, Amorim, Janavs, et al., 1998); (c) a diagnosis of substance abuse within the past six months or lifetime substance dependence; (d) a first-degree relation with schizophrenia-spectrum illness; (e) any psychotropic drug use during the fifteen days preceding their participation in the study; and, (f) reading ability below grade eight equivalent, as assessed by the Wide Range Achievement Test 4th Edition (WRAT-4; Wilkinson & Robertson, 2006).

The SCZ group ($n = 29$) ranged in age from 26 to 56 years and was recruited from the same community. Inclusion criteria for this group were: (a) met DSM-IV criteria for Schizophrenia, Schizophreniform, or Schizoaffective disorder, as confirmed by a MINI and chart review; (b) aged 18 to 60 years old; (c) no change in medication status in the 2 weeks prior to testing, per self-report and/or medical record review; and, (d) normal or corrected-to-normal vision. Exclusion criteria were: (a) any self-reported history of brain damage, psychosurgery, or loss of consciousness and/or other diagnosable neurologic conditions; (b) a diagnosis of substance abuse within the past 6 months or lifetime substance dependence; and (c) reading ability below grade eight equivalent. The Research Ethics Board at St. Joseph's Healthcare

Hamilton approved this study. All participants provided written, informed consent and each was provided compensation of \$10 per hour plus travel costs.

Table 3.1
Sample characteristics of HC and SCZ groups

	HC	SCZ	<i>t</i> or χ^2	<i>p</i>
Age	40.9 (9.0)	44.8 (8.2)	1.73	.09
Sex (n M/F)	15/14	26/3	10.07	< .01
Education	15.3 (2.3)	13.3 (1.8)	3.77	< .01
Parental SES	44.2 (15.3)	39.0 (7.4)	1.63	.11
Diagnosis (n)				
Schizophrenia	-	19	-	-
Schizoaffective	-	10	-	-
Medications (n)				
Typical antipsychotics	-	7	-	-
Atypical antipsychotics	-	24	-	-
Antidepressants	-	10	-	-
Anticonvulsants	-	6	-	-
Anticholinergics	-	3	-	-
Benzodiazepines	-	16	-	-
PANSS Positive ^a	-	40.5 (7.7)	-	-
PANSS Negative ^a	-	36.4 (5.6)	-	-
PANSS General ^a	-	34.9 (3.5)	-	-
PAI-Drug Problems ^a	50.2 (8.3)	54.8 (11.1)	1.81	.08
PAI-Alcohol Problems ^a	46.7 (3.4)	48.2 (10.9)	0.71	.48
WHODAS-II Total ^a	49.4 (8.2)	65.1 (11.6)	6.03	< .01
RBANS Total Index ^b	99.1 (15.5)	80.9 (13.5)	4.86	< .01
WAIS-III eFSIQ ^b	109.7 (14.2)	101.6 (14.2)	2.20	.03
WRAT-4 SC ^b	107.1 (12.3)	89.7 (13.3)	5.22	< .01

Mean (SD); ^aT score; ^bStandard score; **eFSIQ** = Estimated Full-Scale intelligence quotient derived from the Matrix Reasoning and Information subtests of WAIS-III (Sattler & Ryan, 1998); **HC** = healthy control; **PAI** = Personality Assessment Inventory (Morey, 1990); **PANSS** = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); **SES** = Socioeconomic Status (Blishen, Carroll, & Moore, 1987); **WAIS-III** = Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997); **WHODAS-II** = World Health Organization Disability Assessment Schedule 2nd Edition (World Health Organization, 2000); **WRAT4 SC** = Wide Range Achievement Test 4th Edition Sentence Comprehension (Wilkinson & Robertson, 2006)

3.2.2 Baseline Assessment

All participants completed a baseline assessment to characterize their cognitive, clinical, and demographic status. Clinical characteristics and psychodiagnostic information was assessed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Positive and Negative Syndrome Scale (PANSS—patients only; Kay, Fiszbein, & Opler, 1987), and short-form version of the Personality Assessment Inventory (PAI; Morey, 1991). Cognitive functioning was evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) and an abbreviated form of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997). Reading comprehension ability was assessed using the sentence comprehension subtest of the WRAT-4. Information regarding functional status was collected using the World Health Organization Disability Assessment Schedule, 2nd Edition (WHODAS-II; World Health Organization, 2000). Socioeconomic status was estimated on the basis the participants' parental occupation, which was then compared to a normative index of average income as a function of occupation (Blishen, Carroll, & Moore, 1987). To minimize possible fatigue, the baseline assessment was done on a separate day prior to completing the experimental tasks. Group-level data from the baseline assessment are summarized in Table 1.

3.2.3 Face-Vignette Task

Face stimuli were taken from the original Ekman series (Ekman & Friesen, 1976) and depicted the following basic emotions: happy, sad, angry, fear, surprise,

and disgust. All facial stimuli were black and white photographs with hair removed. An equal number of male and female faces were used for each emotion, and the same identity was never repeated within a given emotion category. The situational vignettes were adapted from those used in previous studies (Carroll & Russell, 1996; Green et al., 2007) or were newly constructed for the current study and conveyed the following non-basic emotions: smug, guilty, determined, pain, hopeful, and insulted. The intended emotion for each vignette was confirmed by seven blind, independent raters prior to testing (mean accuracy = 0.90, SD = 0.08) and the observed inter-rater reliability ($\kappa = 0.75$)⁹ indicated substantial agreement among raters (Landis & Koch, 1977). All vignettes were constructed or modified to ensure a Flesch-Kincaid readability level of $\leq$ grade 8 (Kincaid, Fishburne, Rogers, & Chissom, 1975)¹⁰. This helped minimize a potential reading comprehension confound given that all participants demonstrated reading ability above grade 8 (as indexed by the WRAT-4). The face-vignette pairs were matched such that each vignette was discordant with the face in terms of specific emotional category (e.g., angry face paired with pain vignette). However, per Carroll and Russell (1996), the face and situation were consistent with respect to the anticipated “quasi-physical” features of the face (p. 206)—i.e., those superficial features that, in and of themselves, are not necessarily linked to one specific emotion category (e.g., a frown could represent sadness, guilt,

⁹ Given that responses were made on a nominal (i.e., categorical) scale, inter-rater reliability was obtained by computing the arithmetic mean of all kappa (κ) values (Siegel & Castellan, 1988) for each possible rater pair (see Light, 1971).

¹⁰ The Flesch-Kincaid readability statistic takes into account average sentence length and average number of syllables per word within a given passage to compute an approximate grade level.

or disgust depending on the situational context; see Figure 3.1 for example). The specific face-vignette pairs were as follows: happy-smug, sad-guilty, angry-determined, fearful-painful, surprised-hopeful, and disgusted-insulted. Experimental stimuli were presented on a 19" computer monitor using E-prime 2.0 experiment operating software (Psychology Software Tools, Inc.).

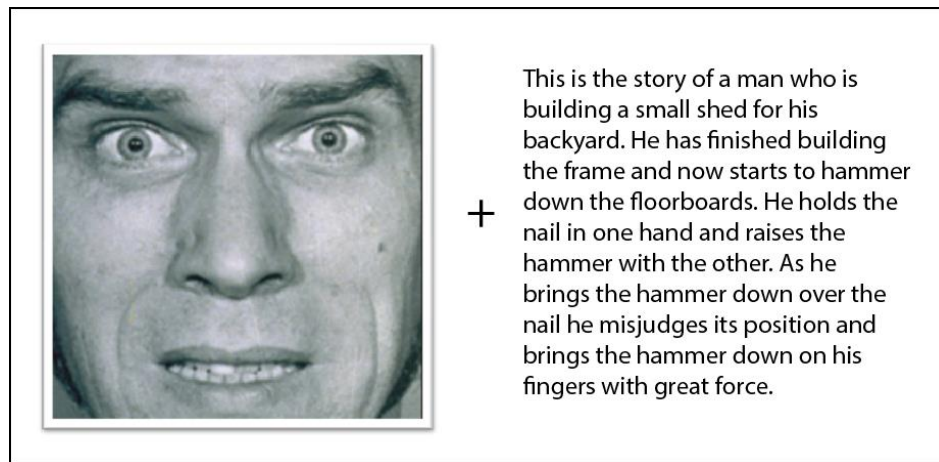


Figure 3.1 Example of a stimulus trial on the FVT. Responding with “fear” to the question, “What emotion is this person feeling” would be coded as a FACE response. Responding with “pain” would be coded as a VIGNETTE response. Any other response would be coded as a RANDOM response.

During the FVT, participants were shown a series of 24 face-vignette pairs and were told that each face represented the subject of the vignette¹¹. To decrease working

¹¹ The original experiment included 12 neutral trials (neutral facial expressions paired with vignettes conveying no emotion) that were interspersed with the emotional trials. Neutral trials were originally included to examine if the hypothesized impairment in effortful, goal-directed responding among SCZ patients would manifest as inappropriately heightened emotional responding—i.e., choosing an emotional response option instead of choosing “no emotion”. However, during the peer review process following submission to *Cognition and Emotion*, both the authors and anonymous referees ultimately agreed that this aim was ancillary to the primary objective of the study, and the resultant data were not instructive to the overall narrative. Nevertheless, to ensure that this experiment can be replicated accurately, it is necessary to report that neutral trials were presented concurrently with emotional trials.

memory load, faces and vignettes were presented simultaneously and remained on the screen until a response was made, allowing participants to freely view and consider all aspects of the stimuli for as long as needed prior to making a decision. Participants read the vignettes aloud to ensure each vignette was read fully and accurately. For each trial, the face-vignette pairs were accompanied by the question, “What emotion is this person feeling?” and participants were asked to provide an answer based on all available information. Responses were made via a labelled keypad using a multiple-choice format. Thirteen possible options were available for each trial: happy, sad, angry, fearful, surprised, disgusted, smug, guilty, determined, pain, hopeful, insulted, and no emotion. Prior to beginning the task, the intended definition of each emotion was reviewed to ensure uniformity across participants. A document with these definitions was available throughout the task and could be consulted at any time. After finishing the FVT, participants completed a basic facial emotion identification test. Participants were shown a series of faces consisting of eight examples of each of the six basic Ekman emotions. The number of male and female faces was balanced across each emotion category.

3.2.4 Data Preparation and Analysis

Between-group differences on the basic face emotion identification task were analyzed with an independent-samples *t*-test using overall accuracy as the dependent variable (DV). On the FVT, responses were recorded as face, vignette, or random responses, and raw count data were converted to proportions. Between-group differences were analyzed using multivariate analysis of variance (MANOVA) with

group as a fixed factor and proportion data for each response type as DVs. Within-group comparisons on the FVT were examined using paired-sample *t*-tests. Effect sizes are reported as partial eta squared (η_p^2) and Cohen's *d*.

Follow-up regression analyses were carried out to determine whether WRAT-4 Sentence Comprehension standard scores or basic face emotion identification accuracy scores either moderated or mediated the relationship between group and FVT responding. This was done to better account for the influence of reading comprehension and basic face emotion processing on group differences in task performance. Moderation analyses were performed first for both variables; mediation analyses were then performed only if non-significant moderation was observed. For the moderation analyses, the continuous moderator variables (WRAT-4 scores or face emotion identification accuracy scores) were centered and used to compute an IV x moderator interaction term. In the first step of the regression, the IV and moderator variables were included as separate predictors of FVT responding. In the second step, the IV x moderator interaction term was included as a separate predictor. If the interaction term coefficient from step 2 was significant, and including the interaction term explained a significant change in variance in the DV (ΔR^2) compared to step 1, then moderation has occurred. Significant moderation effects were decomposed using bivariate correlations between the moderator and DVs at each level of group, and interaction scatter plots were constructed to visualize the regression slopes (Brekke, Kohrt, & Green, 2001).

Mediation analysis, when indicated, was carried out in accordance with the four steps outlined by Baron and Kenny (1986). In step 1 of the mediation analysis, the DV (proportion of face, vignette, or random responses) was regressed on the independent variable (IV; group), ignoring the mediator (WRAT-4 or face emotion identification accuracy scores). In step 2, the mediator was regressed on the IV. In step 3, the DV was regressed on the mediator, controlling for the IV. Finally, in step 4 the DV was regressed on the IV, controlling for the mediator. If the first three steps are statistically significant and step 4 is not, then mediation has occurred (Figure 3.2). When these criteria were met, a bootstrapped version of the Sobel test (re-sampled 10,000 times) was performed *post hoc* in order to examine the statistical significance of the indirect effect of the IV on the DV, through the mediator (Holmbeck, 2002; Preacher & Hayes, 2004).

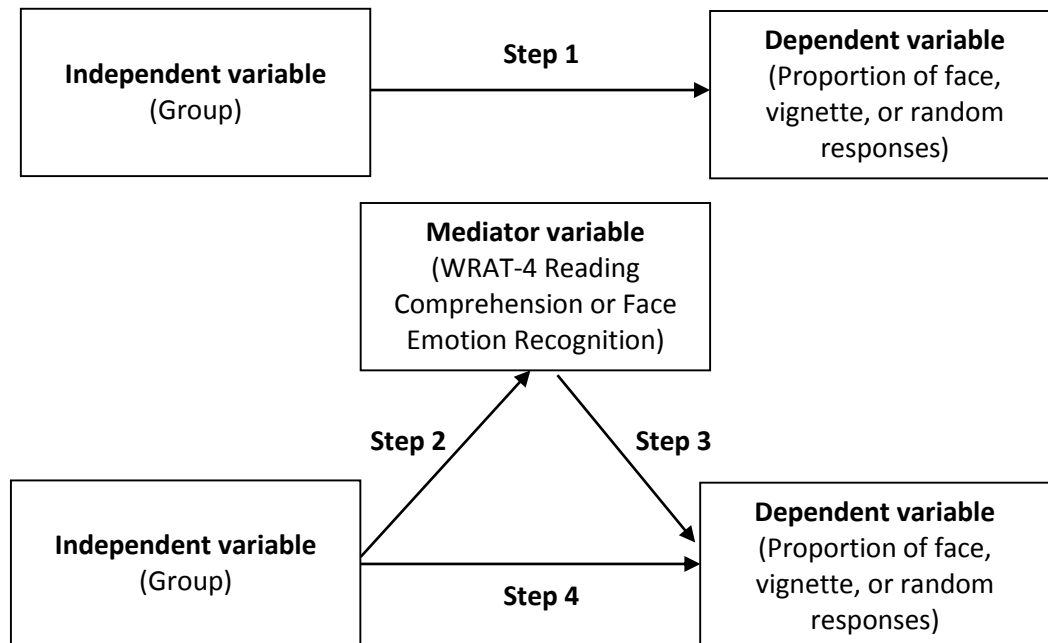


Figure 3.2 Schematic of mediation analysis.

Exploratory bivariate correlational analyses were also performed within each group between FVT responses and the demographic, cognitive, and clinical variables listed in Table 3.1. We adopted a more conservative alpha value of .01 for this analyses to correct for multiple comparisons and minimize the possibility of Type I error.

3.3 RESULTS

3.3.1 Face Emotion Identification Task

A between-group difference was observed for emotion identification accuracy, $t(56) = 2.46, p = .02, d = 0.65$, with the HC group (Mean = 0.84, S.D. = 0.09) outperforming the SCZ group (Mean = 0.78, S.D. = 0.11).

3.3.2 Face-Vignette Task

The omnibus MANOVA showed a significant effect of group overall, $F(2, 555) = 13.26, p < .001, \Lambda = .68, \eta_p^2 = .34$. Follow-up between-group comparisons at each level of response type (using Welch correction) showed that the HC group based a greater proportion of responses on vignettes relative to the SCZ group, $F(1, 45.20) = 27.00, p < .001, \eta_p^2 = .33$, whereas the SCZ group made more face, $F(1, 42.57) = 12.77, p = .001, \eta_p^2 = .19$, and random responses, $F(1, 38.64) = 14.78, p < .001, \eta_p^2 = .21$ (see Figure 3.3). Paired-sample t -tests within the HC group showed a greater proportion of vignette responses compared to both face, $t(28) = 19.77, p < .001, d = 4.71$, and random responses, $t(28) = 21.28, p < .001, d = 5.13$. No difference was found between the proportion of face and random responses, $t(28) = 1.72, p = .10, d$

= 0.34. Within the SCZ group, a greater proportion of vignette responses were made compared to both face, $t(28) = 6.04, p < .001, d = 1.92$, and random responses, $t(28) = 5.84, p < .001, d = 1.96$. As with HCs, no difference was observed between the proportion of face and random responses, $t(28) = 0.26, p = .80, d = 0.08$.

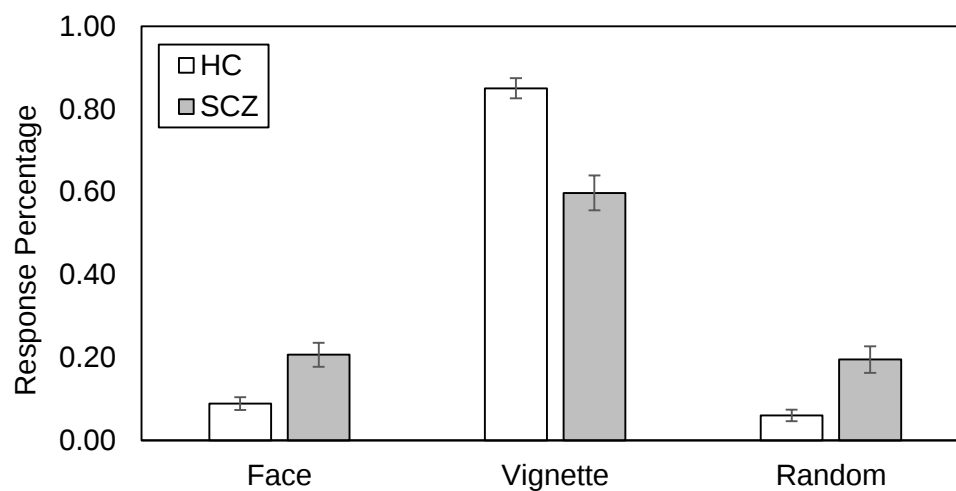


Figure 3.3 Graphical depiction of FVT performance across groups. Response percentage indicates the number of times a particular response type was chosen out of the total number of responses made.

3.3.3 Planned Mediation and Moderation Analyses

A summary of test statistics from the planned moderation and mediation analyses is provided in Tables 3.2 and 3.3, respectively. With respect to reading comprehension ability, regression results indicate that WRAT-4 scores moderated the relationship between group and vignette responding. In the second step of the regression analysis, the group x WRAT-4 interaction term was significant (see Table 3.2), and including this term in the model explained a significant increase in variance

in vignette responding, $\Delta R^2 = .06$, $F(1, 54) = 7.25$, $p = .009$. Follow-up correlations between WRAT-4 scores and vignette responding at each level of group showed a significant positive correlation within the SCZ group ($r = .67$, $p < .001$), but not in the HC group ($r = .32$, $p = .10$). In conjunction with the scatter plot shown in Figure 3.4, this demonstrates that reduced vignette responding in the SCZ group was most pronounced among patients with lower reading comprehension ability.

Table 3.2
Summary of planned moderation analyses

	WRAT-4 ^a Moderator			Face Accuracy ^b Moderator		
	β	t	p	β	t	p
Face responses						
IV	-.24	-1.79	.08	-.36	-2.90	< .01
Moderator	-.58	-3.13	< .01	-.35	-2.26	.01
IV x Moderator	.31	1.80	.08	.14	0.94	.35
Vignette responses						
IV	.28	2.65	.01	.41	4.59	< .01
Moderator	.80	5.54	< .01	.65	5.74	< .01
IV x Moderator	-.36	-2.69	.01*	-.18	-1.57	.12
Random responses						
IV	-.20	-1.54	.13	-.28	-2.86	.01
Moderator	-.67	-3.84	< .01	-.65	-5.14	< .01
IV x Moderator	.26	1.59	.12	.13	1.04	.30

^a Standard scores from WRAT-4 Sentence Comprehension subtest; ^b Overall accuracy from basic face emotion identification task; * Denotes significant moderation; Abbreviations: **IV** = independent variable; **β** = standardized coefficient

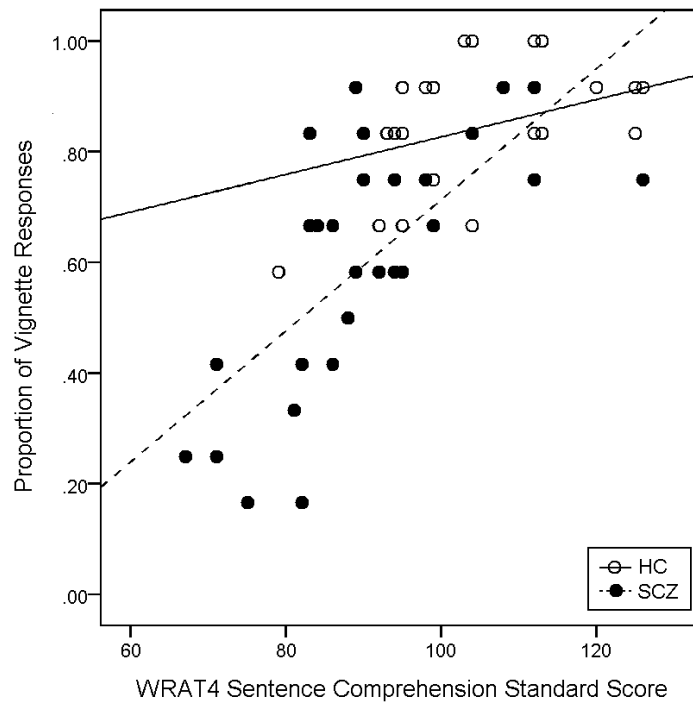


Figure 3.4 Interaction scatter plot depicting reading comprehension ability (as indexed by WRAT-4 sentence comprehension standard scores) as a moderating variable in the relationship between group and vignette responding.

WRAT-4 scores did not moderate the relationship between group and either face or random responding. Accordingly, WRAT-4 scores were examined as a potential mediator for each of these two response categories. Results indicate that the relationship between group and random responding was mediated by WRAT-4 reading comprehension ability. As shown in Table 3.3, the standardized regression coefficient between group and random responding decreased when controlling for WRAT-4 reading comprehension ability (step 4). The other conditions of mediation were also met: group was a significant predictor of random responding (step 1) and WRAT-4 reading comprehension (step 2), and WRAT-4 reading comprehension was a significant predictor of random responding while controlling for group (step 3).

Importantly, follow-up analysis of the indirect effect of group on random responding through WRAT-4 reading comprehension scores via the bootstrapped Sobel test confirmed significant mediation (99% CI: -.15, -.03). WRAT-4 scores did not mediate the relationship between group and face responding (Table 3.3). Basic facial emotion identification accuracy did not moderate (Table 3.2) or mediate (Table 3.3) the relationship between group and any category of responding.

Table 3.3
Summary of planned mediation analyses

	WRAT-4 ^a Mediator			Face Accuracy ^b Mediator		
	β	t	p	β	t	p
Face responses						
Step 1 (DV:IV)	-.43	-3.57	< .01	-.43	-3.57	< .01
Step 2 (M:IV)	.59	5.04	< .01	.31	2.46	.02
Step 3 (DV:M, IV)	-.35	-2.55	.01	-.26	-2.13	.04
Step 4 (DV:IV, M)	-.23	-1.68	.10	-.35	-2.84	.01
Random responses						
Step 1 (DV:IV)	-.45	-3.84	< .01	-.45	-3.84	< .01
Step 2 (M:IV)	.56	5.04	< .01	.31	2.46	.02
Step 3 (DV:M, IV)	-.48	-3.72	< .01	-.57	-5.69	< .01
Step 4 (DV:IV, M)	-.19	-1.46	.15*	-.28	-2.78	.01

^a Standard scores from WRAT-4 Sentence Comprehension subtest; ^b Overall accuracy from basic face emotion identification task; *Denotes significant mediation, per Baron & Kenny (1986) and bootstrapped Sobel test (Preacher & Hayes, 2004); **DV** = dependent variable; **IV** = independent variable; **M** = mediator; β = standardized coefficient

3.3.4 Exploratory Moderation/Mediation Analysis

No correlations were significant within the HC group for any variables listed in Table 3.1. In the SCZ group, significant correlations were observed between WAIS-III eFSIQ and both vignette responses ($r = .59, p = .001$) and face response ($r = -.49, p = .006$), such that lower IQ in patients was associated with less vignette and more face responding. In light of these associations, exploratory regression analyses

were performed to investigate if WAIS-III eFSIQ moderated or mediated the relationship between group and face or vignette-based responding. Results indicate that estimated IQ moderated the relationship between group and face responding. In the second step of the regression analysis, the interaction term between group and IQ was significant (see Table 3.4), and including this term in the model explained a significant increase in variance in face responding, $\Delta R^2 = .06$, $F(1, 54) = 4.92$, $p = .03$. Follow-up correlations between IQ and face responding at each level of group showed a significant negative correlation in the SCZ group ($r = -.49$, $p = .006$), but not in the HC group ($r = -.12$, $p = .52$). In conjunction with the scatter plot shown in Figure 3.5a, this demonstrates that increased face responding in the SCZ group was most pronounced among patients with lower IQ.

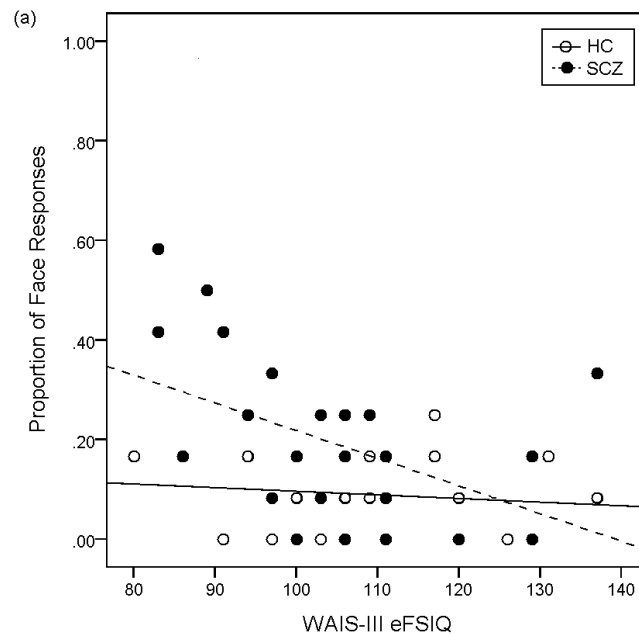
Regarding vignette responses, the regression analyses showed that estimated IQ also moderated the effect of group on vignette-based responding. In the second step of the regression analysis, the interaction term between group and IQ was significant (see Table 3.4), and including this term in the model explained a significant increase in variance in vignette responding, $\Delta R^2 = .07$, $F(1, 54) = 7.07$, $p = .01$. Follow-up correlations between IQ and vignette responding at each level of group showed a significant positive correlation in the SCZ group ($r = .59$, $p = .001$), but not in the HC group ($r = .15$, $p = .45$). In conjunction with the scatter plot shown in Figure 3.5b, this demonstrates that reduced vignette responding in the SCZ group was most pronounced among patients with lower estimated IQ.

Table 3.4

Summary of exploratory WAIS-III eFSIQ moderation analyses

	β	t	p
Face responses			
IV	-.34	-3.01	.004
Moderator	-.58	-3.58	.001
IV x Moderator	.35	2.22	.031*
Vignette responses			
IV	.48	4.81	.000
Moderator	.62	4.36	.000
IV x Moderator	-.37	-2.66	.010*

IV = independent variable; β = standardized coefficient; **WAIS-III eFSIQ** = estimated full-scale IQ from abbreviated Wechsler Adult Intelligence Scale (3rd Edition); * Denotes significant moderation



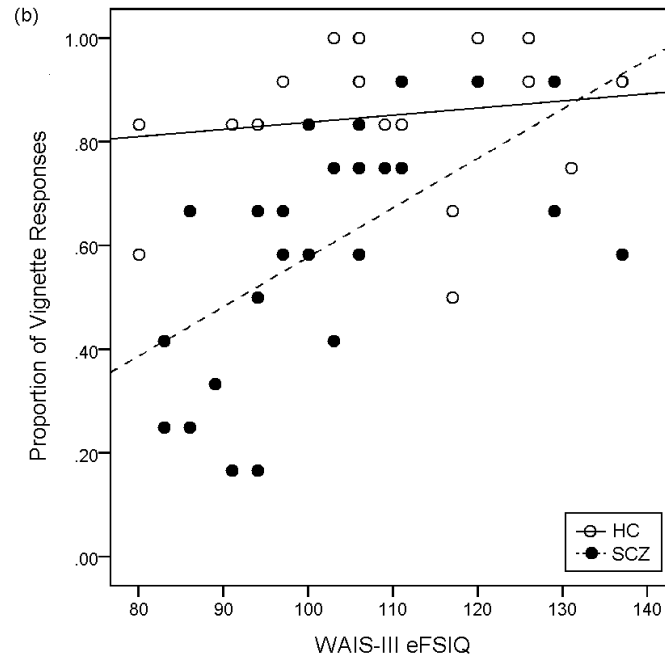


Figure 3.5 Interaction scatter plots depicting WAIS-III eFSIQ as a moderating variable in the relationship between group and (a) face responding and (b) vignette responding.

3.4 DISCUSSION

The current study examined how patients with SCZ reconcile conflict between competing stimuli that impel effortful, contextual versus automatic emotional responding. Participants completed the FVT, which required them to use information gleaned from either faces (automatic) or vignettes (effortful) when making emotional judgments. Importantly, the FVT was modified from previous versions to minimize working memory confounds. Moreover, we examined the influence of reading comprehension, basic facial emotional identification ability, and IQ on FVT performance via mediation and moderation analysis.

Consistent with our hypothesis, the SCZ group demonstrated less vignette responding and more face responding relative to the HCs. These data offer tentative support for the assertion that effortful and automatic emotional processing may be in a state of imbalance in SCZ, as predicted by neural systems models of the disorder (i.e., dorsal stream deficiency; Christensen & Bilder, 2000; Giacco, 2006). Specifically, patients may have difficulty executing behaviours that rely on goal-directed, effortful emotional processing when confronted with a competing stimulus that signals a more automatic emotional response. The observed reduction in vignette responding in the SCZ group also replicates previous research (Green et al., 2007). This is notable as the current protocol was modified in order to minimize working memory demands and ensure that vignette readability was consistent with a minimum cut-off for participants' reading comprehension ability. Our replication under these circumstances strengthens the original finding and bolsters the notion that patients with SCZ have difficulty deploying effortful, goal-directed emotional processing resources in service of overriding or tempering more reactive, automatic responding. Further support comes from the simultaneous increase in face responding among SCZ patients, which was not observed by Green et al. (2007).

Previous findings were extended by identifying and examining certain cognitive factors that may influence the differential pattern of automatic (face) versus effortful (vignette) emotional processing across groups. First, reading comprehension ability moderated the relationship between group and vignette responding, such that reduced vignette responding in the SCZ group was most pronounced among patients

with lower reading comprehension scores (see Figure 3). This suggests that diminished effortful emotion processing on the FVT in patients may have partly depended on their reduced ability to understand and extract the intended meaning from the emotional vignettes. Similarly, estimated IQ moderated the relationship between group and both vignette and face responding. Specifically, individuals with SCZ who also had lower IQ made more face and less vignette responses. This suggests that variability in IQ may be critical in determining the degree of imbalance between effortful and automatic emotional processing in patients with SCZ. Indeed, it is plausible that patients with unaffected IQ are better equipped to self-monitor and correct maladaptive patterns of thought and behaviour (driven by impulsive, automatic emotional responding) by instantiating voluntary, controlled emotional processing. This would be consistent with research showing that intelligence is an important predictor of symptom severity (Brill et al., 2009) and functional outcome (Leeson et al., 2009; Munro et al., 2002). At a broader level, these results suggest that the imbalance between effortful and automatic emotional responding in SCZ may not be a core feature of the disorder given its dependence on other dimensions beyond diagnostic category—i.e., reading comprehension and intelligence.

Interestingly, despite group differences in basic facial emotion identification ability, this factor did not differentially affect the pattern of FVT responding across groups. This appears to run counter to the results of Green et al. (2007), who found that facial emotion recognition was an important predictor of vignette responding. However, Green et al. included face identification accuracy as a standalone predictor

in their regression model and did not examine how it interacted with group, as was done in the current moderation analysis. Thus, although facial emotion recognition may influence the pattern of FVT responding, as per Green et al., it does not appear to differentially affect HC and SCZ groups.

As with IQ, certain dimensions of psychopathology or symptomatology may be associated with a disproportionate reliance on automatic emotional processing relative to HCs. It has been suggested that persecutory delusions in SCZ reflect a heightened automatic attentional bias towards socially threatening stimuli (Green & Phillips, 2004). Thus, on the current task, patients whose clinical presentation was characterized by elevated persecutory delusions may have been more susceptible to over-valuing threatening facial affect cues when generating responses. With this in mind, an exploratory correlational analysis was completed that examined the relationship between face response percentage on trials depicting socially threatening stimuli (i.e., angry and fearful faces) and aspects of clinical symptomatology that reflect persecutory delusions (i.e., the delusional ideation and suspiciousness scales from the PANSS and the Paranoia scale from the PAI). This analysis showed a moderate positive correlation between face responding on angry face trials and PANSS-delusional ideation ($r = .40, p = .03$). This suggests that disproportionate reliance on automatic emotional responding may be particularly robust in the context of socially threatening situations among patients who are prone to delusional ideation. Along with the moderating effect of IQ, these findings speak to the heterogeneity inherent in SCZ samples and highlights the importance of using

caution when interpreting purely group-level effects in SCZ research. Indeed, examining categorical, group level differences does not inform whether abnormal patterns of mental processing are dependent on the presence of specific dimensions of psychopathology, or are core features of the diagnostic category.

It is important to note that although SCZ patients utilized vignette information less than controls, both groups made significantly more vignette versus face responses. This suggests that the effortful, controlled emotional processing stream is partly intact in SCZ, though not at normative levels. In this context, a recent study by Lee et al. (2013) found equivalent influence of situational vignettes on facial affect processing between patients and controls (Lee, et al., 2013). Those authors examined how fearful and surprised vignettes modulated dimensional valence ratings of ambiguous facial expressions in SCZ. They observed a highly comparable degree of vignette-based modulation across patients and controls, such that all participants rated ambiguous faces as more afraid and surprised when they were paired with fear and surprise-inducing sentences, respectively. Similar findings were reported by Chung and Barch (2011) using emotional images instead of vignettes. However, an important distinction between these studies and current experiment concerns the degree of response conflict elicited by the stimuli. Both Lee et al. (2013) and Chung and Barch (2011) investigated how emotional-laden contextual cues modulated valence ratings of emotionally ambiguous faces on a dimensional scale. By contrast, the faces and vignettes in the current study signaled categorically different responses, thereby eliciting clear response conflict.

Accordingly, we argue that SCZ-related impairment in effortful, controlled emotional processing is more likely to emerge when another stimulus is present that signals an alternative, automatic emotional response. Recent data from a conceptually similar task appears to support this assertion (Patrick & Christensen, 2013). Using an emotional directed-forgetting task which placed a forget instruction in direct opposition to automatic emotional memory enhancement, Patrick and Christensen (2013) observed that SCZ patients were less able to forget negative words when instructed to do so by the forget cue. The authors suggest this may have reflected a deficit in patients' ability to employ goal-directed, strategic inhibitory mechanisms when confronted with an opposing stimulus that invoked an automatic emotional response.

There are important limitations of the current study that warrant consideration. First, the inclusion of 13 response options per trial allowed for the possibility of random responding. Doing so precluded us from stating with certainty that reduced effortful processing (i.e., vignette responding) among SCZ patients was the direct result of their greater proclivity for responding on the basis of automatic emotional processing (i.e., face responses). Indeed, patients also demonstrated greater random responding, though the relationship between group and random responding was mediated by reading comprehension ability. In future experiments, an alternative approach might include only two response options per trial representing the face and vignette emotion categories. In doing so, one could better determine whether failure to make a vignette response was the direct result of

choosing the facial emotion instead. Second, we did not directly evaluate participants' comprehension of vignettes in isolation, but rather, used WRAT-4 scores as a proxy for reading comprehension ability. Although this is provided a psychometrically valid estimate of reading comprehension, future studies may benefit from having participants make direct emotional judgments on the vignettes in isolation. However, this will need to be balanced with the potential for biased responding that might result from being presented the same vignettes twice—once in isolation and once on FVT trials. Third, it is possible the abnormal ratio of effortful to automatic responding among patients in the current study simply reflected a bias away from the use of verbal cues (vignettes) or towards the use of non-verbal cues (faces) when guiding behaviour. This could be clarified in future experiments by pairing emotional faces with non-verbal stimuli that invoke more effortful emotional processing (e.g., pictorial scenes).

3.5 SUMMARY & CONCLUSIONS

In summary, the current study offers tentative support for the assertion that individuals with SCZ exhibit deficient effortful, goal-directed emotional processing when confronted with countermanding information that impels a more automatic emotional response. These data add to a growing body of research that highlights abnormalities in effortful emotional processing in SCZ, as well as bolsters the results of previous research (Green et al., 2007) by replicating and extending key findings after better accounting for methodological confounds and other cognitive factors. Moreover, the current data offer some measure of validation for behavioural

predictions derived from dual-stream neural models of SCZ (Christensen & Bilder, 2000; Giaccio, 2006; Phillips et al., 2003). However, these results only offer a speculative window in the underlying neural dynamics. Future studies of this nature could provide further validation by employing direct neurobiologic assays in humans. Task-dependent neuroimaging techniques that examine patterns of functional and/or effective connectivity (e.g., dynamic causal modelling) within cortico-limbic circuits would be particularly informative in this regard.

ACKNOWLEDGMENTS

This research was supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research awarded to Regan Patrick. The authors would like to thank Iulia Patriciu, Katie Herdman, and Carolyn Roy for their contributions towards participant recruitment, data collection, and data management. The authors would also like to thank Melissa J. Green at the University of New South Wales for sharing her stimulus materials to help guide our experimental design.

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CHAPTER 4

REDUCED DIRECTED-FORGETTING FOR NEGATIVE WORDS SUGGESTS SCHIZOPHRENIA-RELATED DISINHIBITION OF EMOTIONAL CUES*

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ABSTRACT

Several psychological and neurobiological models imply that patients with schizophrenia (SCZ) are more inclined to utilize emotional cues as response determinants to the detriment of more task-appropriate cognitive or contextual cues. However, there is a lack of behavioural data from human clinical studies to support this assertion. Therefore, it is important to evaluate the performance of persons with SCZ using tasks designed to index the resolution between competing emotional and cognitive determinants of goal-directed behaviour. The current study employed a list-method, emotional directed-forgetting (DF) paradigm designed to invoke inhibitory mechanisms necessary to override emotional memory enhancement for successful task completion. Four psycholinguistically-matched lists were constructed that were comprised of five negative, five positive, and five neutral words. Compared to healthy controls (HC), individuals with SCZ showed a reduced DF effect overall. When broken down according to valence, this effect was only observed for negative words which, in turn, resulted from reduced forgetting of list 1 words following the forget cue. These results indicate that individuals with SCZ were less able to engage strategic inhibitory mechanisms for the purpose of overriding recall of negative stimuli when tasks demands call for such action. Thus, our data support the theoretical assertion that SCZ patients have difficulty utilizing cognitive or contextual cues as determinants of goal-directed behaviour in the face of countermanding emotional cues.

4.1 INTRODUCTION

Deficits in cognitive processing have been well-documented in Schizophrenia (SCZ) (e.g., Heinrichs and Zakzanis, 1998). Similarly, abnormalities in emotional processing have been observed (Anticevic & Corlett, 2012; Tremeau, 2006), although in-the-moment emotional experience appears to be intact (Anticevic *et al.*, 2012; Herbener *et al.*, 2008; Matthews & Barch, 2004). While substantial research has been devoted to exploring these domains independently, interactions between cognitive and emotional processing, and their synergistic contributions to SCZ-related pathology, have been relatively understudied. Further, the majority of studies that have examined this interaction have focused on patients' susceptibility to task-irrelevant emotional distraction while performing a primary cognitive task. The data in this regard are equivocal. Some behavioural and neuroimaging studies suggest greater vulnerability to emotionally salient distraction in SCZ, particularly for negatively-valenced material (e.g., Bentall & Kaney, 1989; Besnier *et al.*, 2011; Dichter *et al.*, 2010; Mohanty *et al.*, 2005; Park *et al.*, 2008; Strauss *et al.*, 2008), whereas others indicate no differential susceptibility (e.g., Anticevic *et al.*, 2012; Anticevic *et al.*, 2011; Demily *et al.*, 2010; Diaz *et al.*, 2011; Gopin *et al.*, 2011). Anticevic *et al.* (2012) have speculated that SCZ-related vulnerability to emotional distraction may hinge on the extent to which a task engages amygdala-prefrontal cortex (PFC) coupling. Specifically, they suggest that the PFC may serve to down-regulate amygdala responsiveness to emotional stimuli, particularly on tasks which are cognitively demanding and the emotional stimuli are task-relevant. In SCZ, they

posit dysfunctional (i.e., weaker) amygdala-PFC coupling. Therefore, greater SCZ-related susceptibility to emotional distraction may only be apparent on cognitively demanding tasks which utilize task-relevant emotional distractions.

The current study hypothesizes that the inappropriate impact of emotional material may be greatest when it antagonizes cognitive or contextual cues. In this vein, studies investigating the resolution of emotional versus contextual determinants of thought or action may benefit from using experimental tasks that pit these determinants against one another in direct competition. The rationale for these assertions is derived from several psychological and neurobiological models that illustrate the reciprocal nature of emotional and cognitive determinants of goal formation, selection and execution. For example, the two-system view of decision making described by Daniel Kahneman and Amos Tversky illustrates how intuition and reasoning are modulated by a dynamic, and opposing, interaction between emotion and cognition (see Kahneman, 2003 for summary). In this framework, the operations of System 1, which are at the core of intuitive judgments, are fast, automatic, and often recruited in response to emotional stimuli. By contrast, the operations of System 2, which form the basis for controlled reasoning, are thought to be slower, more effortful, and involve meta-cognitive mechanisms that help evaluate the quality of one's mental operations and behaviour. Speechley and Ngan (2008) have suggested that emotional stimuli may initially bias decision making towards System 1. However, should dissonance or conflict arise between the two systems, healthy individuals will typically recruit System 2 in order to "initiate a more

thorough consideration of all available evidence” (p. 1212). This implies that System 2 can implement corrective modifications to actions and thoughts that are erroneously based on System 1 when other cues (e.g., contextual features) are recognized as being more task-relevant. Similar dual-stream models of information processing have been put forth in the context of moral reasoning (Greene *et al.*, 2004) and delayed gratification (Metcalf & Mischel, 1999).

Grace (2003) offers a commensurate account of this interaction from a neurobiological perspective. Following a series of single-cell recording experiments in rodents, a cortico-limbic circuit model was developed to explain how contextual and affective elements in one’s environment may influence subsequent behaviour. Specifically, behavioural response selection is modulated by dual-gating influences provided by the hippocampus and amygdala. The hippocampus is considered the default gate which guides behaviour on the basis of contextual demands or past experience, whereas the amygdala acts as an event-related, affective override during instances of elevated emotional arousal. These two gates, while serving different functions, work in concert to select the most appropriate and adaptive behaviour in a given situation.

This model has been extended to suggest an antagonistic, rather than reciprocal, gating relationship in SCZ. Using a prenatal developmental disruption model in rodents, it was observed that the hippocampus has diminished gating influence, resulting in the amygdala receiving nearly unmitigated priority in determining response selection. Thus, a response pattern emerges in which behaviour

is driven primarily by emotional cues at the expense of more appropriate contextual cues (Grace, 2003). A similar conceptualization has been proposed by Christensen and Bilder (2000) and Giaccio (2006) from a cortical evolutionary perspective. Speechely et al. (2008) have also extended their dual-stream model of reasoning to SCZ in a manner consistent with Grace (2003). Specifically, they argue that Stream 2 is no longer preferentially recruited during periods of conflict, and Stream 1 is excessively recruited during heightened emotional states. This combination leads to a breakdown in normal reasoning whereby decision-making is grounded in emotion rather than logic.

Taken together, these models imply that SCZ patients have difficulty prioritizing cognitive or contextual cues as determinants of goal-directed thought and action in the face of countermanding emotional cues. It is important, therefore, to evaluate persons with SCZ using experimental tasks designed to index the resolution between competing emotional and cognitive determinants of goal-directed behaviour. The emotional Stroop task (EST) is often regarded as the quintessential task to examine such emotion-cognition interactions. However, Algom *et al.*, (2004) have noted that the “emotional Stroop effect” is actually a misnomer. Specifically, they argue that the dimensions that are purportedly in competition with one another on the EST (i.e., emotionality and colour) “lack the semantic conflict or agreement that lies at the heart of the classic Stroop effect” (p. 325). As such, employing the EST to investigate competition between emotional and cognitive response determinants is a conceptually flawed approach because there is no direct antagonism between the two

dimensions. Thus, the EST does not pit emotion against cognition *per se*, but rather, is another task which explores the effect of extraneous emotional distraction on primary cognitive processing. As an alternative, the current study employed an emotional list-method directed-forgetting (DF) paradigm that more directly places emotional and cognitive response cues in opposition.

In general, DF experiments demonstrate that individuals are able to intentionally forget certain information in favour of target information when cued to do so. In the list-method variant, participants are shown a set of items to study for later recall (i.e., list 1). In the forget condition, they are instructed to forget those items in favour of a subsequent set of study items (i.e., list 2). At recall, participants are asked to recall items from both lists. The forget cue attenuates recall of list 1 and enhances recall of list 2. The facilitation of recall of list 2 items is due to reduced proactive interference from list 1 items after receiving a forget cue. This DF effect has been reliably demonstrated across numerous different stimuli and procedural variants (MacLeod, 1999; David & Brown, 2003; Geraerts & McNally, 2003; Racsmany *et al.*, 2008a; Wylie *et al.*, 2008). For example, MacLeod (1999) demonstrated that even under conditions which manipulated demand characteristics (i.e., participants offered monetary compensation for recalling additional items they were told to forget), participants still exhibited better recall of to-be-remembered versus to-be-forgotten items.

The list-method DF effect (i.e., successful forgetting of items that preceded the forget cue) has been attributed to retrieval inhibition (e.g., Bjork *et al.*, 1998;

MacLeod, 1999; Geraerts & McNally, 2008; Soriano *et al.*, 2009; see Benjamin, 2006 for an alternative account). Levy and Anderson (2002) have characterized such inhibitory mechanisms as part of a broader frontal control network that is recruited to override competition from stimulus-driven, prepotent responding. Inhibiting unwanted to-be-forgotten items, therefore, can be considered analogous to suppressing an overt, prepotent behaviour (Levy & Anderson, 2008). Such prepotent behaviours often occur automatically in response to emotionally-charged stimuli. That is, motivationally significant or meaningful stimuli in one's environment are often given rapid and preferential access to cognitive, sensory, and neural processing resources which, in turn, guides behavioural output (e.g., LeDoux, 2000; Dolan & Vuilleumier, 2003; Garrido *et al.*, 2012). Similarly, emotionally evocative material is often conferred an automatic memory advantage in an effect termed the emotional enhancement of memory (EEM; e.g., Kensinger & Corkin, 2003; Kensinger & Corkin, 2004; Anderson *et al.*, 2006; Sommer *et al.*, 2008). Previous research suggests that this effect arises due to deeper encoding and increased attentional resources being devoted to affectively-salient stimuli (e.g., Doerksen & Shimamura, 2001; Kensinger *et al.*, 2003; Payne & Corrigan, 2007; Nasrallah *et al.*, 2009; Hauswald *et al.*, 2011). Further, this emotionality effect appears to be most prominent for highly arousing, negatively-valenced material (e.g., Kensinger *et al.*, 2003; Kensinger *et al.*, 2004; Steinmetz *et al.*, 2010; for contrasting results, see Kousta *et al.*, 2009). In the context of SCZ, a recent study using emotional pictorial stimuli demonstrated that memory enhancement for negative images did not differ between patients with SCZ

and healthy volunteers (Herbener *et al.*, 2007). However, a systematic review of emotional memory in SCZ is more equivocal with respect to the modulatory effects of valence and arousal (Herbener, 2008). Nevertheless, modifying the DF task to include emotional content is well-suited for the current study's objectives as it places the forget cue instruction in direct opposition to the EEM effect. In other words, strategic inhibition must override prepotent emotional memory enhancement for successful task completion.

Relatively few studies have examined DF using emotional stimuli in healthy populations. Wessel and Merckelbach (2006) observed a reliable DF effect at recall using lists comprised of both negative and neutral words, and this effect was not modulated by emotional valence. This has since been replicated using positive words (Itoh, 2011) and autobiographical memories (Barnier *et al.*, 2007). In contrast, others have observed that emotional stimuli are resistant to DF (Payne & Corrigan, 2007), with some data indicating that this effect may be stronger for negatively-valenced material (e.g., Minnema & Knowlton, 2008). Thus, it appears DF is possible for emotional stimuli in healthy individuals, although this may be reduced when stimuli are negatively valenced. These results beg the question, however, whether clinical populations with known susceptibilities to emotional perturbations would demonstrate similar competencies with respect to strategically forgetting emotionally evocative stimuli. Indeed, studies evaluating this phenomenon among patients with major depression and borderline personality disorder have shown reduced inhibition of negative or aversive stimuli (Power *et al.*, 2000; Domes *et al.*, 2006).

A handful of studies have previously explored DF among persons with SCZ. These studies have shown a reduced DF effect relative to healthy participants, which has been attributed to dysfunctional inhibitory control processes (Müller *et al.*, 2005; Racsmany *et al.*, 2008b; Soriano *et al.*, 2009; for contrasting results, see Sonntag *et al.*, 2003). To date, however, no studies have explored *emotional* DF performance in SCZ patients. Thus, in the context of models suggesting poor effortful, strategic response execution in the face of competing emotional cues signalling alternative responses, we hypothesized that (1) SCZ participants would exhibit a reduced DF effect overall relative to healthy volunteers, and (2) the DF effect would be disproportionately reduced for negatively-valenced material.

4.2 METHODS

4.2.1 Participants

The healthy control (HC, $n = 29$) group ranged in age from 24 to 59 years old and were recruited from online and community advertisements in the greater Hamilton, Ontario, Canada area (see Table 4.1 for demographic information). To be included in the study HCs were between 18 and 60 years of age and had normal or corrected-to-normal vision. Exclusion criteria included: (a) self-reported history of brain damage, psychosurgery, loss of consciousness, and/or other diagnosable neurologic conditions; (b) an Axis-I psychiatric disorder as revealed by the Mini International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998); (c) a diagnosis of substance abuse within the past six months or a lifetime history of substance dependence; (d) a first-degree relation with a schizophrenia-spectrum

illness; (e) psychotropic drug use during the fifteen days preceding their participation in the study; and (f) reading ability below a grade eight equivalent as assessed by the Wide Range Achievement Test 4th Edition (WRAT4; Wilkinson & Robertson, 2006).

The SCZ group ($n = 31$) ranged in age from 26 to 56 years old and were recruited from two separate outpatient clinics in Hamilton (see Table 4.1 for clinical and demographic information). Inclusion criteria for this group were that participants: (a) be voluntary and able to provide appropriate consent; (b) meet DSM-IV criteria for Schizophrenia, Schizophreniform or Schizoaffective disorder, as confirmed by a MINI and chart review; (c) be between 18 and 60 years-old; (d) be clinically and pharmacologically stabilized for at least 2 weeks prior to their participation in the study; and (e) have normal or corrected-to-normal vision. Exclusion criteria for patients with SCZ were: (a) any self-reported history of brain damage, psychosurgery, loss of consciousness and/or other diagnosable neurologic conditions; (b) a diagnosis of substance abuse within the past 6 months or a lifetime history of substance dependence; and (c) a reading ability below a grade eight equivalent as assessed by the WRAT-4. The Research Ethics Board at St. Joseph's Healthcare Hamilton approved this study. All participants provided voluntary, written consent to participate and they were provided compensation of \$10 per hour plus travel costs.

Table 4.1
Sample characteristics of HC and SCZ groups

	HC	SCZ	<i>F</i> or χ^2	<i>p</i>
Age	40.9 (9.0)	44.8 (8.2)	2.98	.09
Sex (<i>n</i> M/F)	15/14	27/4	8.93	< .01
Education ^a	15.3 (2.3)	13.3 (1.8)	14.22	< .01
Handedness (<i>n</i> R/L/A)	25/4	28/1/2	3.91	.14
Parental SES ^a	44.2 (15.3)	39.0 (7.4)	2.64	.11
Diagnosis	-	-	-	-
Schizophrenia		20		
Schizoaffective		11		
Medications (<i>n</i>)				
Typical antipsychotic	-	9	-	-
Atypical antipsychotic	-	25	-	-
Antidepressant	-	11	-	-
Anticonvulsant	-	21	-	-
Anticholinergic	-	3	-	-
PANSS Positive ^a	-	40.5 (7.7)	-	-
PANSS Negative ^a	-	36.4 (5.6)	-	-
PANSS General ^a	-	34.9 (3.5)	-	-
BARS ^a	-	0.9 (1.6)	-	-
SAS ^a	-	2.7 (3.3)	-	-
PAI-Drug Problems ^a	50.2 (8.3)	54.8 (11.1)	3.27	.08
PAI-Alcohol Problems ^a	46.7 (3.4)	48.2 (10.9)	0.48	.49
WHODAS-II Total ^a	49.4 (8.2)	65.1 (11.6)	36.32	< .01
RBANS Total Index ^b	99.1 (15.5)	80.9 (13.5)	23.61	< .01
WAIS-III eFSIQ ^b	109.7 (14.2)	101.6 (14.2)	4.82	.03

Mean (SD); ^aT score; ^bStandard score; **WHODAS-II** = World Health Organization Disability Assessment Schedule 2nd Edition (World Health Organization, 2000); **SES** = Socioeconomic Status (Blishen, Carroll, & Moore, 1987); **MINI** = Mini Neuropsychiatric Interview (Sheehan, Lecrubier, Sheehan, Amorim, Janavs, et al. 1998); **PANSS** = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); **BARS** = Barnes Akathisia Scale (Barnes, 1989); **SAS** = Simpson Angus Scale (Simpson & Angus, 1970); **PAI** = Personality Assessment Inventory (Morey, 1990); **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); **WAIS-III** = Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997); **eFSIQ** = Estimated Full-Scale intelligence quotient derived from the Matrix Reasoning and Information subtests of WAIS-III (Sattler & Ryan, 1998); **WRAT4** = Wide Range Achievement Test 4th Edition (Wilkinson & Robertson, 2006)

4.2.2 Materials

Four 15-item wordlists were constructed containing five neutral, positive, and negative words obtained from the Affective Norms for English Words (ANEW; Bradley & Lang, 1999). Different words were chosen for each list, with each list being psycholinguistically matched according to mean word length, frequency, arousal and valence ratings. Given that arousal level appears to be an important moderator in the emergence of EEM, all emotional items were rated highly on this dimension (i.e., mean arousal rating of ≥ 7.1 per list on a 9-point scale, with 1 being low arousal and 9 being high arousal). The word lists and their associated psycholinguistic ratings are provided in Appendix A.

4.2.3 Experimental Procedure

Prior to the experimental session, all participants completed a baseline assessment to characterize their neuropsychological functioning and clinical status (see Table 4.1). In the list-method DF task, participants were shown two different 15-word lists in random order on a computer screen (3 seconds per word) within each condition to study for later recall. The two conditions differed according the cues given immediately following list 1 (L1). In the remember condition, participants were told to remember as many words as possible while in the forget condition participants were told that L1 was just for practice and should be forgotten, and that the next list was the real study list. Following list 2 (L2), participants engaged in a 90-second distracter task to minimize primacy and recency effects. This consisted of counting upwards by three or four digits as quickly as possible. Following the distracter task,

they were asked to recall as many words as possible from L1 and L2 by writing them down in any order on a sheet of paper. The remember condition was always presented first in the testing session as this avoided the need for further instruction to participants that they would not be deceived again (Soriano *et al.*, 2009). Several other unrelated experimental tasks (none of which were verbal learning or memory tests) were administered between remember and forget conditions to limit inter-list contamination at recall. The duration of this inter-condition interval was approximately 2.5 hours.

4.2.4 Data Preparation & Analysis

Primary statistical analyses were performed on DF scores (refer to Table 4.2 for raw recall scores). DF scores were calculated by subtracting L1 recall from L2 recall (Soriano *et al.*, 2009). As such, higher positive DF scores reflect a stronger DF effect. This calculation was performed in each condition (i.e., remember and forget) and at each level of valence. Given that this difference score can reflect either L1 inhibition, L2 facilitation, or a combination of both, it is important to quantify the differential contributions of these two processes to the overall DF score. Thus, separate indices of inhibition and facilitation were computed. An index of inhibition (IOI) was obtained by subtracting L1 recall in the forget condition from L1 recall in the remember condition (Racsmany *et al.*, 2008b). Larger positive IOI values indicated greater inhibition of L1 items following the forget cue. Similarly, an index of facilitation (IOF) was obtained by subtracting L2 recall in the remember condition from L2 recall in the forget condition. In this way, larger positive IOF values

suggested greater facilitation of L2 recall following the forget cue. Error scores were also recorded as intrusions and repetitions (Note: no between-group differences were observed on either of these variables). In terms of statistical analyses, the specific predictions made by our *a priori* hypotheses were examined via planned directional contrasts. Effects sizes are reported as Cohen's *d*.

Table 4.2
Mean items correctly recalled across valence, condition, list, and group

		HC		SCZ	
		List 1	List 2	List 1	List 2
Remember	Overall	4.07 (1.87)	4.14 (1.88)	2.58 (1.67)	2.68 (1.80)
	Negative	1.62 (1.12)	1.76 (1.12)	1.00 (0.97)	0.77 (0.99)
	Positive	1.45 (0.87)	1.72 (0.84)	0.97 (0.87)	1.13 (1.02)
	Neutral	1.03 (0.94)	0.76 (0.91)	0.61 (0.95)	0.77 (0.76)
Forget	Overall	2.24 (1.70)	5.38 (2.14)	1.74 (1.32)	3.00 (1.98)
	Negative	0.72 (0.70)	1.72 (1.00)	0.74 (0.82)	0.87 (0.85)
	Positive	0.93 (0.88)	2.07 (0.96)	0.61 (0.67)	1.35 (1.05)
	Neutral	0.62 (1.01)	1.59 (1.42)	0.39 (0.72)	0.77 (0.92)
Mean (SD)					

4.3 RESULTS

To test the hypothesis that patients with SCZ would exhibit a reduced DF effect overall relative to HCs, planned orthogonal contrasts were performed using DF scores collapsed across valence. The between-group contrast (coefficients: HC = 1, SCZ = -1) was significant within the forget condition only, $t(58) = 3.12$, $p = .003$, $d = .80$ (see Figure 4.1), reflecting larger DF scores for the HC group. The within-group contrast (coefficients: Remember = -1, Forget = 1) was significant in the HC group only, $F(1, 28) = 23.62$, $p < .001$, $d = 1.23$, though the SCZ group showed a similar, albeit reduced, effect at trend levels, $F(1, 30) = 3.97$, $p = .056$, $d = .60$. Taken

together, these contrasts suggest that although both groups exhibited a DF effect, this effect was attenuated in the SCZ group.

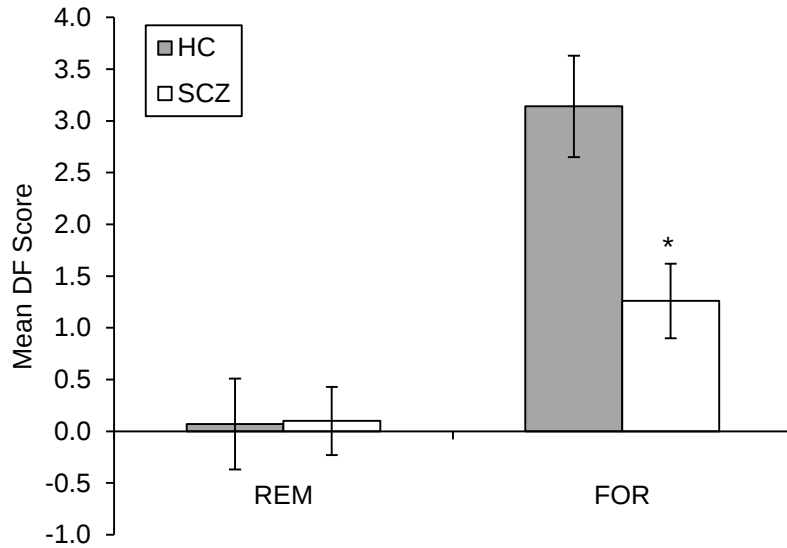
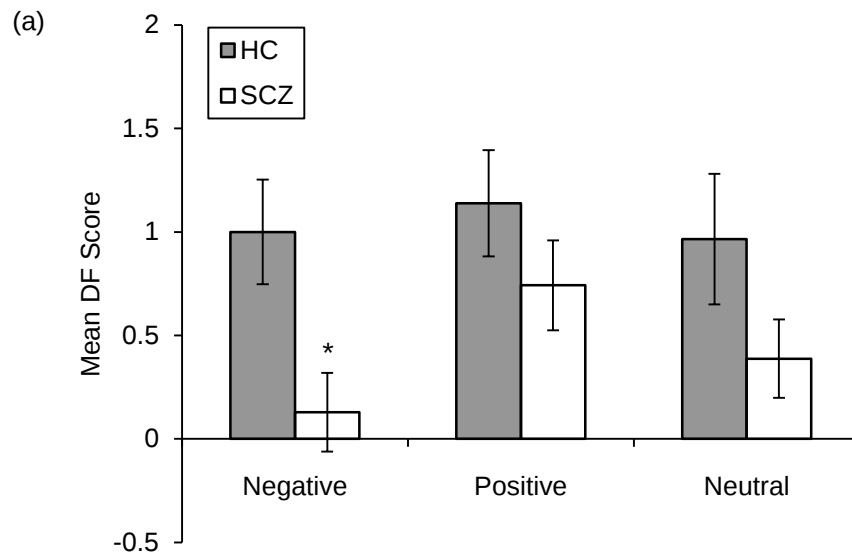


Figure 4.1 Graphical depiction of the significant group x condition interaction using mean directed-forgetting (DF) scores (collapsed across valence) as the primary dependent variable. DF scores were calculated by subtracting the number of correctly recalled items in list 1 from the number of correctly recalled items in list 2 (DF = L2 – L1). Abbreviations: REM = remember condition; FOR = forget condition; HC = healthy control; SCZ = schizophrenia. $*t(58) = 3.12, p = .003, d = .80$.

To test the hypothesis that patients with SCZ would exhibit a disproportionately reduced DF effect for negative words, planned orthogonal contrasts were performed using DF scores separated according to valence in the forget condition only. The within-group contrast (coefficients: Negative = -2, Positive = 1, Neutral = 1) was significant at trend levels in the SCZ group, $F(1, 30) = 3.85, p = .059, d = .47$, but not the HC group, $F(1, 28) = .02, p = .88, d = .04$. Similarly, the between-group contrast (coefficients: HC = 1, SCZ = -1) was significant for negative words, $t(58) = 2.78, p = .007, d = .71$, but not positive, $t(58) = 1.18, p = .24, d = .31$,

or neutral words, $t(58) = 1.60$, $p = .12$, $d = .41$ (see Figure 4.2a). Taken together, these contrasts show a disproportionate reduction in directed-forgetting for negative words in patients with SCZ relative to HCs and, to a lesser extent, relative to other valence categories.

To ascertain whether group differences for negative words was the result of reduced forgetting of L1 or reduced facilitation of L2 in the SCZ group, independent-samples t -tests were performed on IOI and IOF scores for negative words. This revealed a significant between-group difference on IOI only, $t(58) = 2.05$, $p = .045$, $d = .53$ (see Figure 4.2b), suggesting the reduced DF score for negative words in the SCZ group was the result of diminished forgetting of L1 negative words following the forget cue. Interestingly, patient and control groups appear to demonstrate equivalent lack of L2 facilitation for negative words following the forget cue.



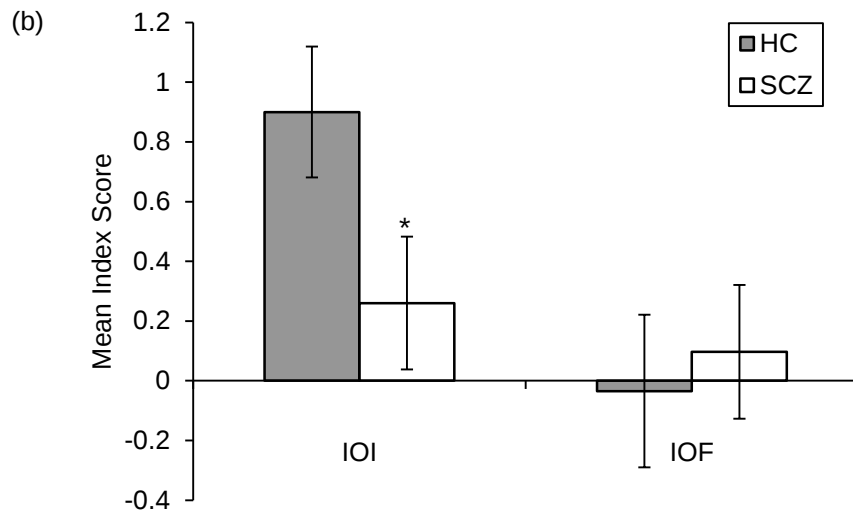


Figure 4.2 (a) Graphical depiction of mean directed-forgetting (DF) scores across group and valence in the forget condition. DF scores were calculated by subtracting the number of correctly recalled items in list 1 from the number of correctly recalled items in list 2 ($DF = L2 - L1$). A significant between-group difference was noted for negative words in the forget condition only. $*t(58) = 2.78, p = .007, d = .71$. (b) Graphical depiction of mean index of inhibition (IOI) and index of facilitation (IOF) scores for negative words only in the forget condition. IOI scores were calculated by subtracting the number of correctly recalled items from list 1 in the forget condition from the number of correctly recalled items from list 1 in the remember condition (i.e., $IOI = L1R - L1F$). IOF scores were calculated by subtracting the number of correctly recalled items from list 2 in the remember condition from the number of correctly recalled items from list 2 in the forget condition (i.e., $IOF = L2F - L2R$). A significant between-group difference was noted for IOI scores only. $*t(58) = 2.05, p = .045, d = .53$. Abbreviations: HC = healthy control group; SCZ = schizophrenia group.

An additional correlational analysis was performed within the SCZ group to determine if any aspect of their PANSS-rated symptomatology or neuropsychological status was related to either their reduced DF or IOI scores for negative words. With respect to symptomatology, none of these correlations were statistically significant. Soriano *et al.* (2009) observed that when their SCZ group was separated according to patients with and without hallucinations (as indicated by PANSS scores), those with hallucinations showed greater inhibitory deficits. We performed a similar analysis

and observed no main effects or interaction when using DF, IOI, or IOF scores as dependent variables. Concerning neuropsychological variables, a significant positive correlation was observed between negative DF scores and the RBANS Visuospatial Index ($r = .38, p = .03$).

4.4 DISCUSSION

The current study sought to examine how individuals with SCZ deploy goal-directed cognitive processing resources in the face of countermanding emotional cues. A list-method emotional DF paradigm was used which places strategic inhibitory mechanisms in opposition to the emotional enhancement of memory. That is, a task-appropriate response determinant (the forget cue) was placed in conflict with an emotional determinant which signaled an opposing response (emotional enhancement of memory). Based on previous research, it was hypothesized that persons with SCZ would exhibit a reduced DF effect overall. Further, we predicted a disproportionately reduced DF effect for negative words.

In line with these predictions, the SCZ group showed a reduced DF effect overall when scores were collapsed across valence. This is consistent with previous research in SCZ using both item- (Müller *et al.*, 2005) and list-method (Racsmány *et al.*, 2008b; Soriano *et al.*, 2009) DF paradigms. Moreover, negative DF scores in the SCZ group were reduced relative to the relative to the HC group and, to a lesser extent, relative to other valence categories (see Figure 1). Importantly, this valence-selective reduction in DF scores appears to have been driven primarily by reduced

forgetting of L1 negative words following the forget cue, as evidenced by differential group performance across IOI, but not IOF scores (see Figure 2). This is similar to what has previously been observed in other clinical samples that are thought to have inhibitory dysfunction, such as borderline personality disorder (Domes *et al.*, 2006) and obsessive-compulsive disorder (Wilhelm *et al.*, 1996). This pattern of results suggests that individuals with SCZ were less able to engage strategic inhibitory mechanisms for the purposes of overriding recall of negative words when tasks demands called for such action.

Unexpectedly, both patient and control groups exhibited a lack of L2 facilitation for negative words following the forget cue. This indicates that the DF effect for negative words was not wholly intact for the control group either as their successful forgetting of L1 items was not associated with the expected concomitant facilitation of L2 items. Previous studies have shown a disrupted list-method DF effect associated with negative stimuli in healthy volunteers (see Minnema & Knowlton, 2008); however, notable methodological differences make direct comparisons with the current data challenging to interpret. Given that the current experiment interspersed negative, positive, and neutral items within the same list, it is reasonable to suggest that the expected facilitation effects after successful forgetting might not been valence-specific. That is, the forgetting of L1 items in one valence category may have translated into L2 facilitation that spilled over into other valence categories due to a general reduction in proactive interference. This may account for the observation that the HC group, and to a lesser extent the SCZ group,

demonstrated L2 facilitation when items were not separated according to valence (see overall values in Table 2). Although this is speculative at this juncture, it offers an interesting avenue for further investigation.

Although we did not directly examine a neurological mechanism for the observed effects in the current study, functional neuroimaging studies offer insight in this regard. For example, a recent fMRI experiment in healthy volunteers observed a higher recognition rate for to-be-forgotten negative versus neutral stimuli. Moreover, the intention to forget negative stimuli, whether successful or not, was associated with widespread activity across a distributed right hemisphere network, including the middle frontal gyrus, middle temporal gyrus, parahippocampal gyrus, precuneus, and cuneus. By contrast, the intention to forget neutral stimuli was associated with right lingual gyrus activity only (Nowicka *et al.*, 2011). These findings suggest that intentionally suppressing negative information is more effortful at both a cognitive and neural level. Another study (also in healthy volunteers) explored ERP effects associated with emotional directed-forgetting and found that the forget cue was associated with an enhanced frontal positivity regardless of whether it followed negative or neutral stimuli, though it was slightly smaller for forget cues that followed negative stimuli (Hauswald *et al.*, 2011). A source modelling analysis revealed that this forget-cue-related positivity for negative stimuli originated in the medial prefrontal cortex. Collectively, these imaging results suggest that our SCZ group may have had difficulty recruiting sufficient neural resources (perhaps within the prefrontal cortex) needed to intentionally suppress recall of negative words. Indeed,

this would be consistent with the assertion that internally-generated inhibitory memory mechanisms arise from a frontal-mediated executive control network that is recruited to override competing, stimulus-driven responding (Levy & Anderson, 2002). Furthermore, this is congruent with data suggesting aberrant PFC-amygdala integration in SCZ (Anticevic *et al.*, 2012).

Regardless of the precise mechanism, this type of speculation highlights the need for future studies to directly examine the neural underpinnings of this disturbance in SCZ via task-dependent functional neuroimaging. Such an approach will more closely link the behavioural phenomenon with a plausible biological substrate. This will be critical in advancing the breadth of knowledge concerning the neuropathology underlying impaired mental processes in SCZ and, in turn, lead to empirically-validated targets for future therapeutic endeavors.

The current study did not find an association between DF scores and any PANSS-related symptomatology in the SCZ group. This observation is perhaps not surprising as our sample consisted of clinically stable outpatients and PANSS T-scores were generally low. Further, this is consistent with the majority of previous research which has examined such correlations (e.g., Sonntag *et al.*, 2003; Müller *et al.*, 2005). That said, Soriano *et al.* (2009) observed that when SCZ patients were dichotomized according to the presence or absence of hallucinations, those with hallucinations showed greater inhibitory deficits relative to patients without hallucinations and HCs. We were unable to reproduce these results in the current study. Although the exact reason for this discrepancy is not known, it may have been

due to differential sample characteristics between the studies (e.g., mean education level was much lower in their sample), or the modulatory effect of emotion that was unique to the current study.

4.5 SUMMARY & CONCLUSIONS

Within the context of models suggesting a disturbance in resolving conflict between emotional and cognitive determinants of action in SCZ, these results suggest that individuals with SCZ have a reduced capacity to utilize task-appropriate contextual cues when faced with competing emotional ones. Based on the current data, this effect appears to be confined to negatively arousing stimuli. Thus, the current data extends the scope of psychological models concerning such emotion-cognition interactions in SCZ (e.g., Speechley *et al.*, 2008), as well as offers some measure of validation for complementary neurobiological theories that are currently lacking in direct behavioural evidence from human clinical samples (e.g., Christensen & Bilder, 2000; Grace, 2003).

ACKNOWLEDGMENTS

This research was supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research awarded to Regan Patrick. The authors would like to thank Iulia Patriciu, Katie Herdman, and Carolyn Roy for their contributions towards participant recruitment, data collection, and data management.

APPENDIX A

Psycholinguistic characteristics of the word lists

	List 1	List 2	List 3	List 4	<i>p</i>
Length					
NEG	7.6 (1.5)	6.2 (1.5)	4.8 (1.5)	5.6 (2.1)	.09
POS	5.8 (1.6)	6.6 (2.3)	6.0 (2.4)	7.0 (4.1)	.89
NEU	5.6 (1.3)	4.8 (1.6)	5.6 (1.8)	4.4 (1.1)	.52
Frequency					
NEG	10.8 (7.1)	25.6 (28.2)	31.9 (53.5)	12.2 (29.5)	.64
POS	32.8 (32.6)	22.8 (15.1)	11.2 (9.3)	29.0 (24.7)	.46
NEU	32.8 (39.5)	105.8 (122.8)	39.2 (48.6)	116.0 (216.3)	.64
Arousal					
NEG	7.3 (0.5)	7.1 (0.4)	7.2 (0.5)	7.1 (0.9)	.94
POS	7.5 (0.2)	7.4 (0.4)	7.1 (0.3)	7.6 (0.4)	.08
NEU	3.8 (0.4)	3.7 (0.3)	4.1 (1.0)	3.8 (0.5)	.65
Valence					
NEG	1.9 (0.5)	2.1 (0.5)	2.2 (0.4)	1.9 (0.5)	.70
POS	8.0 (0.5)	8.1 (0.5)	7.9 (0.4)	8.1 (0.4)	.96
NEU	5.1 (0.1)	5.1 (0.1)	5.1 (0.1)	5.1 (0.1)	.96

Mean (SD); Note: *p*-value represents simple main effect of list. Abbreviations: NEG=negative; POS=positive; NEU=neutral

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CHAPTER 5

NEUROPHYSIOLOGICAL CORRELATES OF EMOTIONAL DIRECTED-FORGETTING IN PERSONS WITH SCHIZOPHRENIA: AN EVENT-RELATED BRAIN POTENTIAL STUDY

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ABSTRACT

Recent research has shown that patients with schizophrenia (SCZ) exhibit reduced directed forgetting (DF) for negative words, suggesting impaired ability to instantiate goal-directed inhibition in order to suppress emotional memory encoding. However, disrupted inhibition is not the only possible mechanism by which patients could manifest reduced emotional DF. Therefore, the primary objective of the current study was to use event-related brain potential (ERP) recordings to investigate alternative hypotheses. ERPs were recorded while patients and controls completed an item-method DF paradigm using negative and neutral words. The anterior N2 indexed goal-directed inhibition of to-be-forgotten items. The anterior/posterior late positive potential (LPP) indexed emotional memory encoding. The posterior P300 indexed selective rehearsal of to-be-remembered items. The SCZ group did not exhibit a reduced emotional DF effect. Forget cue-induced N2 amplitude was not modulated by group or emotion. LPP amplitude was greater for negative versus neutral words in both groups at anterior sites; however, this emotion effect was seen at posterior sites only in controls. Remember-cue-induced P300 amplitude was greater for cues following negative versus neutral words only in controls. These data did not support the hypothesis that inhibitory processes are disrupted by competing emotional information in SCZ. Moreover, patients' ERP data suggested that they did not exhibit disproportionately heightened encoding of emotional stimuli. Rather, the most prominent ERP abnormality among patients was that they did *not* exhibit enhanced P300 amplitude for remember cues following negative stimuli. These

results suggest diminished ability to enhance targeted memory encoding strategies for emotional stimuli.

5.1 INTRODUCTION

Schizophrenia (SCZ) is characterized by abnormalities in both emotional and cognitive processing. However, the interactive contribution of these domains to SCZ psychopathology has not been studied extensively. To date, investigations of emotion-cognition interactions in SCZ have primarily focused on the effects of extraneous emotional distraction on primary cognitive processing and yielded inconsistent results. Behavioural and neuroimaging research suggests *both* increased vulnerability (e.g., Bentall & Kaney, 1989; Dichter, Bellion, Casp, & Belger, 2010; Mohanty, Herrington, Wenzel, Webb, & Heller, 2005; Park, Park, Chun, Kim, & Kim, 2008; Strauss, Allen, Duke, Ross, & Schwartz, 2008) and normal susceptibility to emotional interference (Anticevic, Repovs, & Barch., 2012; Anticevic, Repovs, Corlett, & Barch, 2011; Demily, Attala, Fouldrin, Czernecki, & Ménard, 2010; Diaz et al., 2011; Gopin, Burdick, DeRosse, Goldberg, & Malhotra, 2011). These apparently discrepant findings may stem from variability in methodology and sample characteristics across studies. However, it is also possible that they result from the fact that previous studies have failed to employ tasks that maximize the antagonistic relationship between cognitive and emotional determinants of behaviour. Such antagonism frequently typifies cognition-emotion interactions in real-world settings (e.g., Metcalfe & Mischel, 1999; Bickel et al., 2007) and may potentiate the likelihood that one will impact the other (Anticevic et al., 2012). That is, patients with SCZ may have difficulty prioritizing cognitive or contextual response cues as

determinants of goal-directed behaviour in the face of countermanding emotional cues that impel an alternative response.

Patrick and Christensen (2013) recently investigated this assertion using an emotional, list-method directed-forgetting (DF) paradigm. Briefly, a list of study items is presented before the memory instruction is given. This instruction designates all prior items as either to-be-forgotten (TBF) or to-be-remembered (TBR), after which a second list of study items is presented. At recall, participants are asked to recall as many items as possible from both lists. The typical finding from DF experiments is that memory for TBR items is better than for TBF items—the DF effect. However, by modifying the DF paradigm to include emotional content, the forget instruction (i.e., the cognitive or goal-directed response cue) is placed in direct opposition to emotional memory enhancement¹² (i.e., the opposing emotional response cue). In other words, the goal-directed behaviour (forgetting) must override a competing, automatic emotional behaviour (emotional memory enhancement) for successful task completion. Using the emotional list-method, Patrick and Christensen (2013) observed a smaller overall DF effect in the SCZ group, consistent with previous research (Müller, Ullsperger, & Hammerstein, 2005; Racsmány et al., 2008a; Soriano et al., 2009). Importantly, patients with SCZ were less able to intentionally forget negative words compared to healthy controls (HC) and relative to positive and neutral words, with list 2 facilitation being equivalent across groups.

¹² Emotionally significant stimuli are often conferred an automatic memory advantage termed the emotional enhancement of memory (e.g., Anderson, Yamaguchi, Grabski, & Lacka, 2006; Kensinger&Corkin, 2003; Kensinger&Corkin, 2004; Sommer, Glächer, Moritz & Büchel, 2008).

These results suggest a deficit in SCZ patients' ability to instantiate a task-relevant, goal-directed behaviour (i.e., memory inhibition of to-be-forgotten words) in service of overriding an opposing, automatic emotional response (i.e., memory enhancement for emotionally negative material).

These data are consistent with recent neurobiological models of SCZ suggesting anomalous regulation of the neural circuits governing emotional reactions versus those governing task-relevant cognitive processing (Anticevic et al., 2012; Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003). However, these data are also clearly behavioural and, at best, offer a strictly inferential window into the functional neurobiology underlying these effects. Elucidating the associated neural dynamics is particularly relevant in the context of emotional DF as there are several distinct putative mechanisms by which patients with SCZ could demonstrate a reduced emotional DF effect. First, patients with SCZ may be deficient in applying strategic inhibitory mechanisms to TBF emotional material, as suggested by Patrick and Christensen (2013). If so, this would provide support for the assertion that patients with SCZ have difficulty implementing goal-directed, cognitive behaviours in the face of competing emotion-laden response cues. By contrast, inhibitory mechanisms might be intact and patients may simply engage in more elaborate encoding of emotional material. This would presumably lead to stronger emotional memory enhancement and, by extension, reduced emotional DF. A third possibility is that patients with SCZ exhibit decreased selective rehearsal of TBR negative items. The selective rehearsal account of DF posits that, upon seeing a remember cue,

participants engage in more elaborate encoding of TBR items, thereby enhancing recognition relative to TBF items. Thus, patients may have difficulty implementing targeted, strategic encoding processes (i.e., selective rehearsal) to aid subsequent memory performance for TBR negative content. Indeed, strong arguments have been put forth suggesting the DF effect primarily reflects increased rehearsal of to-be-remembered items and *not* forget cue-induced strategic inhibition (e.g., Sheard & McLeod, 2005; Benjamin, 2006).

Adjudicating between these competing hypotheses has been complicated at the behavioural level. In contrast, several studies have identified specific neurophysiological correlates of memory inhibition, emotional memory encoding, and selective rehearsal processes in healthy volunteers. These experiments have primarily utilized the *item-method* DF variant as it is more adaptable to ERP techniques. In this variant, participants are shown a series of study items one-at-a-time and are cued to remember or forget each item immediately after it is presented. The typical finding is that subsequent recognition memory for TBR items is better than for TBF items. With this in mind, the primary objective of the current study was to examine item-method, emotional DF using ERP methodology to directly examine the alternative predictions described above and better characterize the neurocognitive mechanisms associated with abnormal emotional DF in SCZ.

5.1.1 ERP Correlates of Forget Cue-Induced Memory Inhibition

Results from several ERP studies support the hypothesis that cue-induced, goal-directed inhibition contributes to the DF effect. Yang and colleagues (2012) observed a larger anterior ERP negativity (200 – 300ms) for forget cues associated with successfully forgotten items (i.e., TBF-miss) (Yang, Liu, Xiao, Li, Zeng, Qiu, et al., 2012). This aligns with several other DF studies that have observed distinct electrophysiological activity associated with forget cues at anterior sites (Brandt, Nielsen, & Holmes, 2013; Cheng, Liu, Lee, Hung, & Tzeng, 2011; Hauswald, Schulz, Iordanov, & Kissler, 2010; Paz-Caballero et al., 2004; van Hooff & Ford, 2011). The latency range and scalp topography of the negativity observed by Yang et al. corresponds to the N2 component. This is notable as substantial research suggests the N2 is an index of inhibitory or executive control processes (see Folstein & van Petten, 2008 for review). For example, go/no-go, think/no-think, stop signal, and Erikson flanker tasks all elicit a more pronounced N2 on trials necessitating greater response inhibition (Folstein & van Petten, 2008; Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013). EEG inverse modelling and simultaneous EEG-fMRI analysis indicates that the anterior N2 is generated in medial and/or lateral prefrontal cortices (Huster et al., 2013). This is consistent with fMRI studies implicating frontally-centered inhibitory control mechanisms in intentional memory suppression in DF (Nowicka, Marchewka, Jednorog, Tacikowski, & Brechmann, 2011; Wylie, Foxe, & Taylor, 2008), as well as other cognitive inhibition paradigms (Anderson et al., 2004; Levy & Anderson, 2008; Depue, Curran, & Banich, 2007).

Interestingly, Yang et al. found that the N2 associated with the forget cue was further enhanced following negative pictures, suggesting that forgetting negative material requires greater inhibitory effort. Accordingly, they observed an equivalent behavioural DF effect for both neutral and negative pictures, suggesting this inhibitory mechanism was effective at overcoming automatic emotional memory enhancement. Thus, the anterior N2 component can be considered an electrophysiological signature of cue-induced memory inhibition.

5.1.2 ERP Correlates of Emotional Memory Enhancement

Emotional stimuli are preferentially encoded and retained in memory (Anderson et al., 2006; Kensinger & Corkin, 2003). Several lines of research suggest that the late positive potential (LPP) may be a reliable neurophysiological marker of enhanced emotional memory encoding (Dolcos & Cabeza, 2002; Fröhholz, Jellinghaus, Herrmann, 2011; Palomba, Angrilli, & Mini, 1997). The LPP is a sustained, slow-wave ERP component that typically emerges 300-400ms after stimulus onset and is more prominent in response to emotionally evocative versus neutral stimuli (Fischler & Bradley, 2006; Hajcak, MacNamara, & Olvet, 2010; Moran, Jendrusina, & Moser, 2013). Functionally, the LPP is thought to reflect a sustained increase in attention to, and processing of, intrinsically motivating stimuli (Hajcak et al., 2010). Palomba et al. (1997) detected a more sustained, positive-going waveform spanning the 300-900ms window for emotionally arousing stimuli that were subsequently associated with better recall relative to neutral and low arousing stimuli. Similarly, Dolcos and Cabeza (2002) reported enhanced positivity for

arousing versus neutral pictures over centroparietal sites in the 400-600ms window, which corresponded to improved recognition performance. In their review of emotion-related ERP effects, Olofsson and colleagues (2008) stated that such results “can be interpreted as ERP memory formation effects for affective stimuli” (p. 7). Several item-method DF studies have also observed an enhanced centroparietal LPP waveform for emotional study items that were subsequently better recognized (Bailey & Chapman, 2012; Hauswald et al., 2010; Yang et al., 2012). Interestingly, Brandt et al. (2013) observed a larger LPP for negative words at anterior sites only, suggesting a broader scalp distribution. Thus, there appears to be substantial data to support the LPP waveform as a topographically distributed and reliable neurophysiological signature of emotional memory enhancement.

5.1.3 ERP Correlates of Remember Cue-Induced Selective Rehearsal

Some have suggested that the DF effect results from selective rehearsal of TBR items (Basden, Basden, & Gargano, 1993; MacLeod, 1998). This interpretation is supported by studies showing a distinct remember-cue positivity at centroparietal electrode sites with a latency of approximately 300-400ms after cue onset (Cheng et al., 2011; Hsieh, Hung, Tzeng, Lee, & Cheng, 2009; Paz-Caballero et al., 2004; van Hooff & Ford, 2011; Yang et al., 2012). This latency range corresponds to the P300 component (Polich, 2007), which is likely important given that the P3b subcomponent of the P300 has been linked to attentional allocation and memory encoding (Azizian & Polich, 2007), as well as rote rehearsal (Fabiani et al., 1986, 1990). Indeed, a recent review of the functional correlates of the P300 concluded that

“stimulus encoding that promotes successful memory storage to facilitate retrieval and recognition produces increased P300-like amplitude” (p.2132; Polich, 2007). Accordingly, previous item-method DF research has shown enhanced P300 amplitude following remember cues at centroparietal sites that is associated with stronger subsequent memory for TBR items (Yang et al., 2012). Thus, the posterior P300 component can be considered a neurophysiological signature of remember cue-induced selective rehearsal.

Taken together, these experiments show that specific ERP components can be used to index various underlying cognitive sub-processes of DF, namely goal-directed inhibition (forget cue-induced N2), emotional memory encoding (LPP), and selective rehearsal (remember cue-induced P300). This parsing of underlying processes permits a more direct characterization of how opposing cognitive and emotional processes may be reconciled at a neural systems level. If reduced emotional DF in SCZ results from diminished inhibition of TBF negative items, then we would expect a smaller amplitude anterior N2 waveform for forget cues that follow negative versus neutral items (Hypothesis 1). This would support the assertion that patients with SCZ have difficulty prioritizing cognitive or contextual response cues as determinants of goal-directed behaviour in the face of countermanding emotional cues. However, if inhibitory mechanisms are intact and patients simply engage in greater encoding of emotional material, then we would expect a disproportionately enhanced LPP in response to negative versus neutral study items (Hypothesis 2). Finally, if reduced emotional DF in SCZ results from diminished selective rehearsal of TBR negative

items after receiving the remember cue, then we would expect a smaller amplitude P300 waveform for remember cues that follow negative versus neutral items compared the controls (Hypothesis 3).

5.2 METHODS

5.2.1 Participants

The HC group ($n = 20$) ranged in age from 26 to 61 years and was recruited from the greater Hamilton, ON community via online advertisements. Inclusion criteria for this group included: (a) ages 18 to 65 years; (b) normal or corrected-to-normal vision; and (c) a reading level equivalent to grade 8 according to Wide Range Achievement Test- 4th edition (WRAT-4; Wilkinson & Robertson, 2006). Exclusion criteria included: (a) any self-reported history of brain damage, psychosurgery, or loss of consciousness and/or other diagnosable neurologic conditions; (b) a diagnosable psychiatric disorder as revealed by the Mini International Neuropsychiatric Interview (MINI; Sheehan, Lecrubier, Sheehan, Amorim, Janavs, et al., 1998); (c) a diagnosis of substance abuse within past 6 months or lifetime substance dependence; (d) a first-degree relation with schizophrenia spectrum illness (i.e., Schizophrenia, Schizoaffective, or Schizophreniform disorder); and (e) any psychotropic drug use during the fifteen days preceding their participation in the study.

The SCZ group ($n = 19$) ranged in age from 28 to 56 years and was recruited from two outpatient clinics in Hamilton, ON specializing in treatment and rehabilitation of SCZ. Inclusion criteria for this group were that they: (a) were able to provide voluntary and informed consent, which was evaluated using a modified

version of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR; Applebaum & Grisso, 2001); (b) were aged 18 to 65 years; (c) met DSM-IV-TR criteria for Schizophrenia, Schizophreniform, or Schizoaffective disorder, as confirmed by a MINI interview and chart review; (d) had no change in medication status for at least 2 weeks prior to testing; (e) had normal or corrected-to-normal vision; and (f) had a reading level equivalent to grade 8 according to the WRAT-4. Exclusion criteria included: (a) any self-reported history of brain damage, psychosurgery, or loss of consciousness and/or other diagnosable neurologic conditions; and (b) a diagnosis of substance abuse within the past 6 months or lifetime substance dependence. Sample characteristics for the SCZ and HC groups are shown in Table 5.1. The Research Ethics Board at St. Joseph's Healthcare Hamilton approved this study. All participants provided voluntary, written consent to participate and they were provided compensation of CAN\$10 per hour plus travel costs.

Table 5.1

Sample characteristics of HC and SCZ groups

	HC	SCZ	<i>t</i> or χ^2	<i>p</i>
Age	40.2 (11.6)	44.5 (6.4)	1.44	.16
Sex (<i>n</i> M/F)	8/12	9/10	0.22	.64
Education (years)	16.8 (3.4)	13.9 (2.0)	3.14	< .01
Parental SES	4037 (10.9)	42.0 (8.2)	0.55	.58
WHODAS-II Total ^a	48.3 (4.2)	63.9 (12.2)	5.42	< .01
Diagnosis				
Schizophrenia	-	11	-	-
Schizoaffective	-	8	-	-
PANSS Positive ^a	-	38.9 (6.4)	-	-
PANSS Negative ^a	-	37.2 (7.2)	-	-
PANSS General ^a	-	34.9 (3.5)	-	-
Medications (<i>n</i>)				
Typical antipsychotics	-	3	-	-
Atypical antipsychotics	-	18	-	-
Anticonvulsants	-	6	-	-
Antidepressants	-	8	-	-
Benzodiazepines	-	10	-	-
PAI Alcohol ^a	47.8 (5.5)	52.2 (9.8)	1.74	.09
PAI Drugs ^a	46.3 (5.7)	56.2 (13.6)	2.93	.01
RBANS Total Index ^b	100.7 (15.0)	79.1 (14.9)	4.49	< .01
WAIS-III eFSIQ ^b	116.7 (14.1)	96.6 (15.4)	4.23	< .01
WRAT-4 Reading ^b	105.7 (11.6)	93.8 (8.9)	3.45	< .01

Mean (SD); Statistical values represent between-group differences using Student's *t*-tests or chi-square analysis; ^a T-score; ^b Standard score; **HC** = healthy control; **PAI** = Personality Assessment Inventory (Morey, 1990); **PANSS** = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998); **SCZ** = schizophrenia; **SES** = Socioeconomic Status (Blishen, Carroll, & Moore, 1987); **WAIS-III** = Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997); **eFSIQ** = Estimated Full-Scale intelligence quotient derived from the Matrix Reasoning and Information subtests of WAIS-III (Sattler & Ryan, 1998); **WRAT4** = Wide Range Achievement Test 4th Edition (Wilkinson & Robertson, 2006); **WHODAS-II** = World Health Organization Disability Assessment Schedule 2nd Edition (World Health Organization, 2000).

5.2.2 Baseline Assessment

Prior to the experimental session, all participants completed a baseline assessment to characterize their neuropsychological functioning and clinical status

(see Table 5.1). Clinical characteristics and psychodiagnostic information was assessed using the MINI, Positive and Negative Syndrome Scale (PANSS—patients only; Kay, Fiszbein, & Opler, 1987), and an abbreviated version of the Personality Assessment Inventory (PAI; Morey, 1991). Cognitive functioning was evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), an abbreviated form of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997), and the word reading subtest of the WRAT-4. In addition, functional status was assessed using the World Health Organization Disability Assessment Schedule, 2nd Edition (WHODAS-II; World Health Organization, 2000). To minimize possible fatigue, the baseline assessment was conducted on a separate day prior to completing the experimental tasks.

5.2.3 Emotional DF Task

For the emotional, item-method DF task, two lists of 140 words each were constructed (see Table 5.2 for psycholinguistic characteristics). Words were drawn from the Affective Norms for English Words (ANEW; Bradley & Lang, 1999). One list was designated as the study list and the other as the foil list. Each list contained 70 negative and 70 neutral words. Negative and neutral words from the study list were further broken down into 35 TBR words and 35 TBF words. Participants completed the emotional DF task in an electrically shielded, sound-attenuated chamber. They were seated 100 cm in front of a computer monitor on which stimuli were visually presented. Words were centered on the monitor and displayed in yellow font on a black background. The font size was 42 point with each letter

subtending approximately 0.36° of visual angle horizontally and 0.55° vertically. Words were presented in pseudo-random order so that no more than three words from the same emotion category (i.e., negative or neutral) or instructional set (i.e., TBR or TBF) were shown consecutively. Each stimulus word was presented for 500ms, followed by a blank screen for 1000ms. A cue was then presented that instructed the participants to either remember (“RRRR”) or forget (“FFFF”) the word that was just displayed. Cues remained on the screen for 500ms and were followed by another blank screen for 2000ms, at which point the next word was presented. Participants were asked to remember only words that were followed by the “RRRR” cue and forget the words followed by “FFFF” cue. The study phase was followed by a 10-minute distracter task in which participants completed the Arithmetic subtest of the WRAT-4. A recognition test was then completed in which participants were shown the 140 words from the study list interspersed with the 140 foil words. They were asked to indicate whether each word was “OLD” or “NEW” regardless of whether a word was followed by an “RRRR” or “FFFF” cue during the study phase. Each word remained on the screen until a response was made. Participants responded by button press on one of two buttons positioned under the right or left thumb. One button (labelled “OLD”) signalled that they remembered seeing the word during the study phase, while the other button (labelled “NEW”) signalled that they did not remember seeing the word during the study phase. Assignment of buttons was counterbalanced across participants.

Table 5.2
Psycholinguistic characteristics of study and foil lists

	Study list			Foil list		
	Negative	Neutral	<i>p</i>	Negative	Neutral	<i>p</i>
Valence	2.09 (1.47)	5.00 (1.51)	< .01	2.09 (1.43)	5.01 (1.49)	< .01
Arousal	5.97 (2.54)	4.10 (2.08)	< .01	5.73 (2.57)	4.19 (2.15)	< .01
Dominance	3.77 (2.40)	4.88 (1.71)	< .01	3.73 (2.41)	4.88 (1.72)	< .01
Length	6.71 (1.85)	6.07 (2.11)	.06	6.50 (1.82)	6.79 (1.79)	.09
Frequency	28.24 (66.81)	90.59 (217.26)	.04	21.95 (37.23)	38.75 (57.72)	.05

Mean (SD); *p*-values represent differences between negative and neutral words within each list using Student's *t*-tests

5.2.4 ERP Acquisition & Analysis

During the DF task, the electroencephalogram (EEG) signal was recorded using an ActiveTwo system (BioSemi BV, Amsterdam) from 32 different sites approximately equally spaced across the scalp, positioned according to a modified international 10-20 system (Fp1-Fp2-AF3-AF4-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-T8-C3-Cz-C4-CP5-CP1-CP2-CP6-P7-P3-Pz-P4-P8-PO3-PO4-O1-Oz-O2). The EEG was referenced to a left parietal Common Mode Sense (CMS) active electrode and a right parietal Driven Right Leg (DRL) passive electrode, which formed a feedback loop driving the average potential across the montage as close as possible to the amplifier zero. The EEG was continuously digitized at 512 Hz and low-pass filtered at 128 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids and bandpassed at 0.01- 100 Hz. Continuous data were algorithmically corrected for eye blink artifacts

(Jung, Makeig, Humphries, Lee, McKeown et al., 2000). ERP epochs were from 200ms pre-stimulus to 1000ms post-stimulus. Individual trials containing eye movement artifacts, excessive muscle activity, or amplifier blocking were rejected off-line by visual inspection before time-domain averaging. Mean percentage of trials lost to such artifacts was 15% for patients and 12% controls, which was not a statistically significant difference.

For ERP waveform analysis, N2 and P300 amplitudes were time-locked to instructional cues and were computed for both remember and forget cues at each level of valence. (i.e., TBR-Negative, TBF-Negative, TBR-Neutral, and TBF-Neutral). LPP amplitude was time-locked to study words and was computed for negative and neutral items. The analysis window for each component was determined by inspection of the grand average waveforms (see below). For N2 waveforms, mean amplitudes were computed over a cluster of bilateral anterior electrode sites (Fz, AF3, AF4, F3, F4, FC1, and FC2). For P300 waveforms, mean amplitudes were computed over a cluster of bilateral posterior electrode sites (Pz, CP1, CP2, P3, P4, PO3, and PO4). Given that previous research indicates variable topographic distribution of the LPP waveform (Fischler & Bradley, 2006; Hajcak et al., 2010), mean amplitudes were computed separately for both anterior and posterior electrode clusters. Hemisphere was not included as a factor as previous research has shown negligible or non-systematic effects of laterality for LPP or cue-induced waveforms in similar DF paradigms (e.g., Bailey et al., 2012; Brandt et al., 2013; Hsieh et al., 2009; van Hooff et al., 2011; Cheng et al., 2011).

5.2.5 Statistical Analysis

For behavioural data, a three-way mixed, repeated-measures ANOVA was performed for recognition hit rate, with GROUP (HC and SCZ) as a between-subjects factor, and VALENCE (negative and neutral) and INSTRUCTION (TBR and TBF) as within-subjects factors. False alarms, sensitivity (d'), and response bias (c) were also analysed using a GROUP x VALENCE repeated-measures ANOVA¹³. For ERP data, N2 and P300 waveforms were analysed using a GROUP x INSTRUCTION x VALENCE repeated-measures ANOVA. For LPP waveforms, a GROUP x VALENCE repeated-measures ANOVA was performed separately at anterior and posterior sites. Planned follow-up comparisons were performed within and between groups to examine how forget cue-induced N2, remember cue-induced P300, or study word-induced LPP waveforms were differentially modulated by emotion. Bivariate correlations were performed to examine the association between these ERP components and recognition performance. Separate correlations were also performed within the SCZ group only to characterize any associations between the demographic, clinical, and cognitive variables listed in Table 5.1 and (1) recognition

¹³ INSTRUCTION could not be included as a factor when analyzing false alarms, sensitivity, and response bias because remember and forget instructions were *only* provided in the study list. That is, false alarms could not be broken down according to INSTRUCTION as items from the foil list could not be classified as 'remember' or 'forget'. This also precluded us from computing values for d' and c as a function of INSTRUCTION.

performance, (2) forget cue-induced N2 amplitude, (3) remember cue-induced P300 amplitude, and (4) study word-induced LPP amplitude (all at each level of valence).

5.3 RESULTS

5.3.1 Behavioural Data

Recognition performance is summarized in Table 5.3. The omnibus analysis of hit rate showed main effects of VALENCE, $F(1,37) = 4.79$, $p = .04$, $\eta_p^2 = 0.12$ (negative > neutral), and INSTRUCTION, $F(1,37) = 30.87$, $p < .001$, $\eta_p^2 = 0.46$ (TBR > TBF). A GROUP x INSTRUCTION interaction was also observed, $F(1,37) = 16.57$, $p < .001$, $\eta_p^2 = 0.31$. This reflected better recognition of TBR versus TBF words in the HC group only, $t(19) = 6.73$, $p < .001$, $d = 1.41$ (see Figure 5.1). For false alarms, a main effect of VALENCE was observed, $F(1,37) = 25.00$, $p < .001$, $\eta_p^2 = 0.40$ (negative > neutral), as well as a main effect of GROUP at trend levels, $F(1,37) = 3.38$, $p = .07$, $\eta_p^2 = 0.08$ (SCZ > HC). For sensitivity, main effects of VALENCE (neutral > negative), $F(1,37) = 21.36$, $p < .001$, $\eta_p^2 = 0.37$, and GROUP (HC > SCZ), $F(1,37) = 6.75$, $p = .01$, $\eta_p^2 = 0.15$, were observed. For response bias, a main effect of VALENCE was observed, $F(1,37) = 22.27$, $p < .001$, $\eta_p^2 = 0.38$, with participants generally responding more liberally for negative versus neutral words.

Bivariate correlations within the SCZ group did not reveal any significant associations between demographic, clinical, and cognitive variables listed in Table 5.1 and hit rate at any level of instruction or valence. However, negative correlations were observed between WAIS-III eFSIQ and false alarm rate for negative ($r = -.69$, p

= .001) and neutral words ($r = -.59, p = .007$), as well as a positive correlation between negative d' and both WAIS-III eFSIQ ($r = .68, p = .001$).

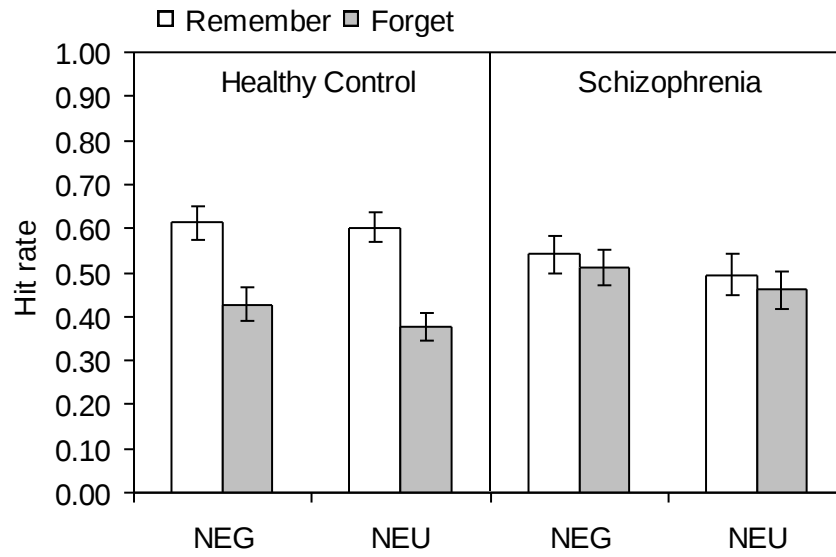


Figure 5.1 Hit rate as a function of group, valence, and instruction. HC = healthy control group; SCZ = schizophrenia group; NEG = negative words; NEU = neutral words. Error bars represent standard error of the mean.

Table 5.3

Recognition performance as a function of group and valence

	Healthy control		Schizophrenia	
	Neutral	Negative	Neutral	Negative
Remember	0.60 (0.15)	0.61 (0.17)	0.49 (0.20)	0.54 (0.18)
Forget	0.38 (0.14)	0.43 (0.17)	0.46 (0.19)	0.51 (0.18)
False alarms	0.22 (0.23)	0.31 (0.17)	0.33 (0.23)	0.43 (0.16)
Sensitivity	0.98 (0.73)	0.61 (0.51)	0.49 (0.47)	0.26 (0.39)
Response bias	0.51 (0.53)	0.25 (0.41)	0.32 (0.58)	0.06 (0.37)

Mean (SD). Negative response bias values signify a tendency toward responding *old* (i.e., liberal), whereas positive values signify a tendency toward responding *new* (i.e., conservative).

Contrary to previous research (Patrick & Christensen, 2013), the SCZ group did not exhibit a disproportionately reduced DF effect for negative words. One

possible explanation for this null effect concerns the symptomatic heterogeneity common among SCZ samples. That is, perhaps only certain dimensions of SCZ psychopathology render persons susceptible to the type of emotion-cognition antagonism predicted here. Although PANSS symptomatology was not associated with emotional DF in SCZ patients, we explored this possibility further by computing indices of internalizing (INT) and externalizing (EXT) psychopathology from the PAI¹⁴ for all patients and included these index scores in an exploratory correlational analysis with recognition hit rate. The EXT dimension reflects a vulnerability for outwardly expressed pathology (e.g., impulsivity, conduct problems, and substance abuse), whereas the INT dimension reflects a tendency to express psychopathology inward (e.g., anxiety and depression) and experience high negative emotionality (Blonigen et al., 2010; Ruiz & Edens, 2008). These two dimensions were chosen on the basis of factor analytic work that suggests they confer vulnerability to a broad range of psychopathology (Blonigen et al., 2010). Importantly, elements of both of these dimensions are commonly seen in the clinical presentation of SCZ patients, with confirmatory factor analysis demonstrating that the SCZ syndrome loads adequately onto both INT and EXT dimensions (Kotov et

¹⁴ To obtain INT and EXT index scores, we computed weighted means using specific subsets of PAI scale T-scores for each dimension. The coefficient weights were derived from parameter estimates from a recent confirmatory factor analysis of the INT/EXT model (Ruiz & Edens, 2008). The INT factor consisted of the following PAI scales: Anxiety (ANX), Anxiety-Related Disorders (ARD), Depression (DEP), Somatization (SOM), Schizophrenia (SCZ), Borderline (BOR), and Paranoia (PAR). The EXT index consisted of the following scales: Drug Problems, Alcohol Problems, Antisocial, Mania, BOR, and PAR. The BOR and PAR scales were included in both index scores because they were shown to load positively onto each factor with similar parameter estimate values (Ruiz & Edens, 2008).

al., 2011; Ruiz & Edens, 2008). Results showed a moderate positive correlation between INT and hit rate for negative TBF items that approached significance using the adjusted alpha value of .01 ($r = .46, p = .04$). This suggests that as patients' level of INT psychopathology increased, their capacity for successfully forgetting negative words may have decreased. No other correlations approached significance.

5.3.2 ERP Data

5.3.2.1. N2 waveform. Inspection of the grand average waveforms indicates N2 peak latency was between 200-350ms for both neutral (Figure 5.2a) and negative (Figure 2b) words. This corresponds to the typical latency range of the N2 component (Folstein et al., 2008) and thus served as the time window for statistical analysis. Omnibus analysis showed a main effect of INSTRUCTION, $F(1,37) = 6.79, p = .01, \eta_p^2 = 0.15$, reflecting the expected larger amplitude negativity for forget versus remember cues. No other main or interaction effects were significant. Planned comparisons also did not reveal any within or between group differences for forget cue-induced N2 amplitude as a function of emotion. Forget cue-induced N2 amplitude did not correlate with recognition performance for TBF words in either group, nor did it correlate with any demographic, clinical, or cognitive variables listed in Table 5.1 within the SCZ group.

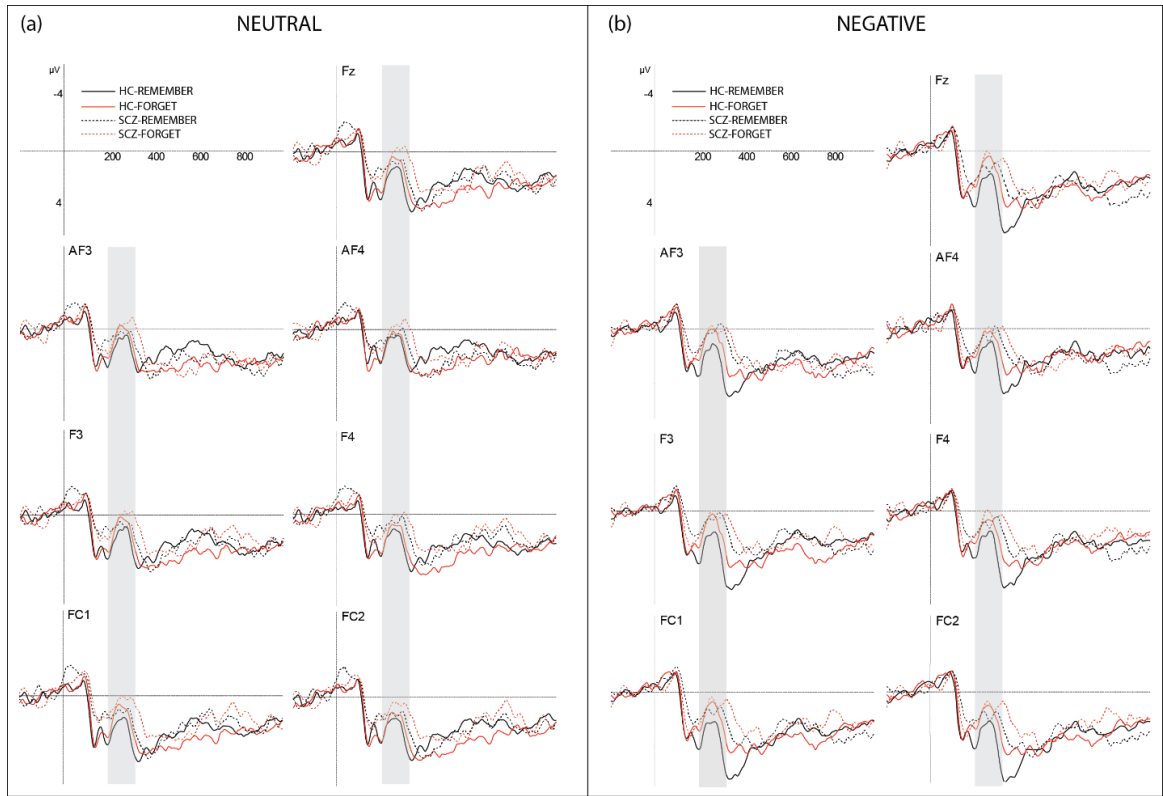


Figure 5.2 Cue-induced ERP waveforms at anterior electrode sites for cues that followed (a) neutral and (b) negative words. The shaded area depicts the analysis window for the N2 component (200-350ms). HC = healthy control group; SCZ = schizophrenia group.

In light of the behavioural findings concerning INT psychopathology and negative TBF items noted above, we examined correlations between forget cue-induced N2 amplitude and INT/EXT psychopathology at each level of valence. This analysis showed an interesting dissociation as a function of INT/EXT psychopathology. Specifically, small-to-moderate negative correlations were observed between N2 amplitude and INT psychopathology for cues that followed both negative ($r = -.22$) and neutral ($r = -.19$) words, whereas correlations were negligible for EXT psychopathology for each valence category (see Appendix A). These data suggest that INT psychopathology may be associated with general inhibitory deficits.

It is important to note, however, that these correlations were not statistically significant (all $p > .10$), which is perhaps not surprising in light of the relatively small *ns*. Accordingly, these correlations are most appropriately viewed as very preliminary, and most certainly require replication with larger samples.

5.3.2.2. LPP waveform. Inspection of the grand average waveforms indicates a sustained LPP waveform beginning at approximately 400ms after the presentation of study words at anterior (Figure 5.3a) and posterior (Figure 5.3b) sites. Accordingly, LPP amplitude was computed for negative and neutral study words across two successive 200ms time windows beginning at 400ms post-stimulus onset at anterior and posterior sites. Omnibus analysis showed a main effect of VALENCE, such that negative words elicited a more positive-going LPP wave form at anterior sites in the 400-600ms, $F(1,37) = 8.43$, $p < .01$, $\eta_p^2 = 0.19$, and 600-800ms, $F(1,37) = 5.54$, $p = .02$, $\eta_p^2 = 0.13$, time windows. In addition, a GROUP x VALENCE interaction was significant at trend levels in the posterior region during the 600-800ms window, $F(1,37) = 3.85$, $p = .057$, $\eta_p^2 = 0.09$ (see Figure 5.3). Follow-up comparisons within this time window showed that among HCs, LPP amplitude was larger for negative versus neutral words, $t(19) = 2.46$, $p = .02$, $d = 0.46$, whereas within the SCZ group, LPPs were not significantly different across negative and neutral words, $t(18) = 0.57$, $p = .58$, $d = 0.13$. A between-group difference in this time window was also observed for neutral LPPs, with the SCZ group showing more positive LPP amplitude for neutral words, $t(37) = 2.34$, $p = .03$, $d = 0.75$. As with N2 waveforms, LPP amplitude (in any of the time windows noted above) did not correlate with subsequent memory

performance, nor did it correlate with any demographic, clinical, or cognitive variables listed in Table 5.1 within the SCZ group. In addition, exploratory correlation analysis did not reveal any notable patterns of dissociation in LPP amplitude as a function of INT/EXT pathology or emotional valence in any time window (Appendix A).

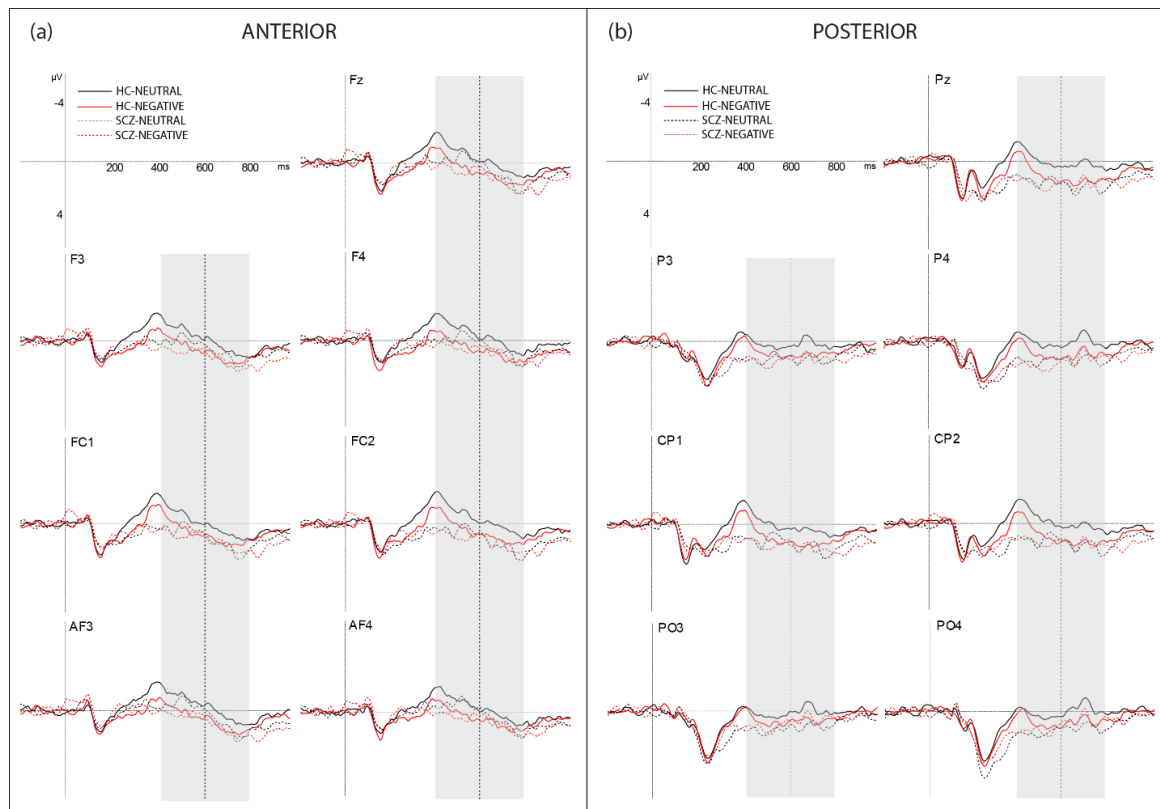


Figure 5.3 LPP waveforms for negative and neutral words at (a) anterior and (b) posterior electrode sites. The shaded area depicts the successive 200ms analysis windows for the LPP component (400-600ms and 600-800ms). HC = healthy control group; SCZ = schizophrenia group.

5.3.2.3. *P300 waveform.* Inspection of the grand average waveforms indicates P300 peak latency was between 250-450ms for neutral (Figure 5.4a) and negative (Figure 5.4b) words. This corresponds to the typical latency range of the P300 waveform (Polich, 2007), and thus was used as the time window for statistical analysis. Omnibus analysis showed a main effect of INSTRUCTION, $F(1, 37) = 17.97, p < .001, \eta_p^2 = 0.33$, reflecting the expected larger amplitude waveform for remember versus forget cues. Planned comparisons within each group showed that remember cue-induced P300 amplitude was significantly greater for cues that followed negative versus neutral words in the HC group, $t(19) = 2.68, p = .02, d = 0.44$, but not the SCZ group, $t(18) = 0.56, p = .59, d = 0.13$. Planned comparisons between groups were all non-significant. As with N2 and LPP waveforms, remember cue-induced P300 amplitude did not correlate with recognition performance for TBR items, nor did it correlate with any demographic, clinical, or cognitive variables listed in Table 5.1 within the SCZ group. In addition, exploratory correlation analysis did not reveal any notable patterns of dissociation in P300 amplitude between INT and EXT pathology or negative and neutral cues (Appendix A).

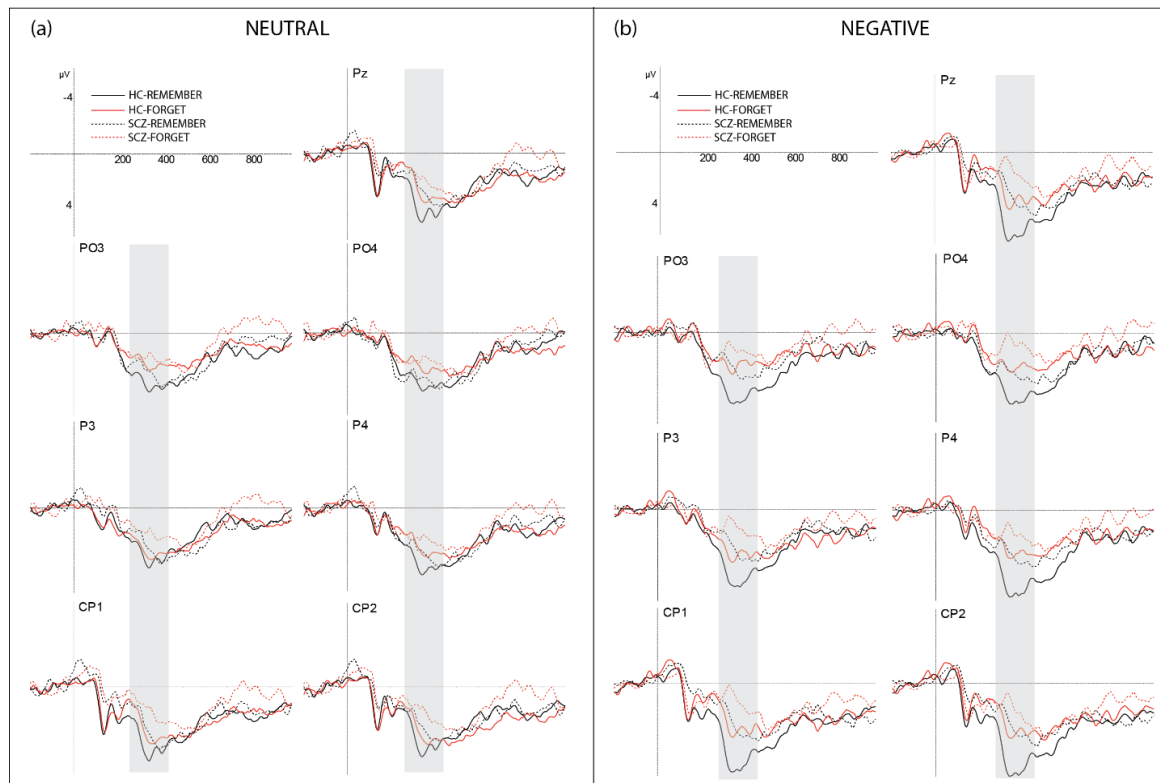


Figure 5.4 Cue-induced ERP waveforms at posterior electrode sites for cues that followed (a) neutral and (b) negative words. The shaded area depicts the analysis window for the P300 component (250-450ms). HC = healthy control group; SCZ = schizophrenia group.

5.4 DISCUSSION

The primary objective of the current study was to extend previous research by investigating ERP correlates of emotional DF in SCZ. The motivation for this study was twofold. First, we aimed to clarify whether abnormalities in emotional DF in SCZ reflects decreased goal-directed inhibition, increased emotional memory enhancement, or decreased selective rehearsal of emotional items. Second, we sought to further elucidate the neural correlates of emotional DF abnormalities in patients with SCZ. In doing so, the N2, LPP, and P300 waveforms were examined as they

have been validated as neurophysiological indices of inhibition, emotional memory encoding, and rehearsal processes, respectively.

5.4.1 Behavioural Data

At a behavioural level, TBR words were associated with a higher hit rate than TBF words—the standard DF effect. This effect was modulated by group in that patients with SCZ did not exhibit a DF effect. Deficient DF in SCZ is consistent with the list-method DF data from Patrick and Christensen (2013) and several other non-emotional DF studies in SCZ (Miller et al., 2005; Racsmany et al., 2008; Soriano et al., 2009). Patients with SCZ also had reduced sensitivity for discriminating between study and foil words compared to HCs, as indicated by their overall higher false alarm rate (at trend levels) and lower d' . Response bias did not differ significantly between groups. Across both groups, negative words were associated with a higher hit rate and false alarm rate, as well as more liberal response bias relative to neutral words. These findings suggest that negative words were better remembered than neutral words (i.e., emotional memory enhancement), though this may have been due to both reduced sensitivity and lower threshold for responding OLD to negative words.

Contrary to our hypothesis and previous research (Patrick & Christensen, 2013), the SCZ group did not exhibit a disproportionate reduction in DF for negative words. Rather, patients showed generally deficient DF compared to HCs. One potential factor contributing to this discrepancy concerns the symptomatic heterogeneity common among SCZ samples. That is, there may be certain

dimensions of psychopathology within the diagnostic boundaries of SCZ that, when elevated, render an individual more susceptible to the type of emotion-cognition antagonism hypothesized here. By examining purely categorical, group-level effects, we may have masked such vulnerability. In this vein, we observed a positive correlation between INT psychopathology and hit rate for TBF negative words in SCZ patients. This suggests that patients with higher levels of INT symptoms showed higher levels of interference by emotionally negative words on the DF effect. Consistent with this observation, previous studies using clinical samples characterized by internalizing psychopathology (e.g., major depressive disorder, anxiety disorders, and eating disorders) have observed reduced DF for emotional words that were illness-related or personally relevant (Power, Dalgleish, Claudio, Tata, & Kentish, 2000; Tekcan, Caglar, Topcuoglu, & Yucel, 2008; Wilhelm, McNally, Baer, & Florin, 1996; Wingefeld et al., 2013). Thus, it seems plausible that predominant INT psychopathology may be associated with greater difficulty overcoming emotional response cues when task demands (i.e., forget cue) call for such action. This raises an interesting question as to whether previously observed SCZ-related emotional DF deficits (Patrick & Christensen, 2013) are specific to SCZ, or whether several forms of INT psychopathology, including SCZ, could show such deficits. More generally, these data highlight one of the pitfalls of anchoring cognitive psychopathology research within current diagnostic taxonomy (Bilder, Howe, & Sabb, 2013) and demonstrates the importance of exercising caution when interpreting categorical, group-level effects.

The discrepancy between the current study and the findings of Patrick and Christensen (2013) might have also resulted from different DF paradigms being used in each study. Patrick and Christensen used the list-method variant with a recall memory test, whereas the current study used the item-method with a recognition memory test. The item-method was used in the current study because it is readily adapted to ERP techniques. However, this may have resulted in the two studies measuring slightly different inhibitory processes. Specifically, it has been postulated that the list-method DF paradigm elicits *retrieval* inhibition during the recall test phase by virtue of TBF items being rehearsed and encoded to the same extent as TBR items prior to the forget cue being presented (Bjork, 1989). By contrast, the item-method is thought to index *encoding* inhibition during the study phase (Rizio & Dennis, 2013). That is, study items are held in working-memory until the forget cue is presented, at which point participants initiate inhibitory processes that suppress further encoding of TBF items. With this distinction in mind, it is possible that retrieval and encoding inhibition are not equally impaired in SCZ. In this context, previous research has shown that patients with SCZ have varying levels of impairment across tasks that invoke different types of memory inhibition. For example, Racsmany et al. (2008) observed a significant impairment in what they termed intentional inhibition using a list-method DF task relative to controls; however, patients and controls demonstrated equivalent performance on a different task that elicits incidental inhibition (i.e., retrieval practice task). Thus, it is plausible that patients' ability to override emotional memory enhancement might vary as a

function of which DF variant is used. Although speculative at this juncture, this possibility offers an interesting avenue for future research into the nature of SCZ-related abnormalities in DF.

5.4.2 ERP Data

5.4.2.1. Goal-directed inhibition: The N2 waveform. At anterior sites, forget cues elicited an enhanced N2 negativity compared to remember cues. Yang et al. (2012) observed a similar effect of instruction over frontal sites that peaked at approximately 270ms in healthy volunteers. The authors related this negativity to the N2 component, which appears to be sensitive to inhibitory processes engaged by several other cognitive tasks (Folstein & van Petten, 2008). In conjunction with source modelling that suggests the anterior N2 is generated in medial and/or lateral frontal cortices (Huster et al., 2013), these findings are consistent with the assertion that inhibitory mechanisms associated with intentional memory suppression are part of a broader frontal control network used for stimulus-driven response inhibition (Levy & Anderson, 2002; Depue, 2012). Moreover, this interpretation supports theories of DF that invoke goal-directed inhibition during encoding (Rizio & Dennis, 2013; Zacks, Radvansky, & Hasher, 1996).

Importantly, however, the current data show that the main effect of instruction on N2 amplitude was not modulated by group. Moreover, forget cue-induced N2 wave forms were not differentially modulated for cues following negative versus neutral words in either HCs or SCZ patients. These ERP data parallel the equivalent behavioural DF effect for negative and neutral words in both groups.

Collectively, these results suggest that (1) the overall reduced DF effect among patients did not result from diminished memory inhibition on this task and (2) goal-directed inhibitory mechanisms were not affected by emotion in patients with SCZ. The former runs counter to a number of behavioural studies that have attributed reduced DF in SCZ to disrupted inhibition (Soriano et al., 2009; Racsmany et al., 2008; Muller et al., 2005). More importantly, the latter does not support the pattern of emotion-cognition dysregulation predicted by Hypothesis 1. That is, at the neurophysiological level, the SCZ group as a whole did not exhibit disproportionate difficulty deploying goal-directed cognitive resources in the face of countermanding emotional response determinants. However, interesting preliminary correlational data suggest that higher levels of INT psychopathology in patients may be associated with a general inhibitory deficit, as evidenced by small-to-moderate negative correlations between forget cue-induced N2 amplitude and INT psychopathology at each level of valence. As noted earlier, these data are very preliminary and replication is clearly needed to better ascertain the reliability of this association.

5.4.2.2 Emotional memory enhancement: The LPP waveform. Contrary to Hypothesis 2, none of the LPP data are suggestive of disproportionately high emotional memory encoding in the SCZ group. At anterior sites, negative words elicited a larger LPP amplitude across the entire 400-800ms window, and this effect was not modulated by group. At posterior sites, only the HC group exhibited more positive LPP amplitude for negative versus neutral words in the 600-800ms window. When anterior and posterior electrode data are interpreted together it appears that,

although the emotion-induced LPP waveform was present for both groups, it was diminished and more topographically restricted in the patient group. Previous research has similarly shown a reduced late positivity in response to emotional words at posterior sites in patients versus controls (Kuperberg, Kreher, Swain, Goff, & Holt, 2011). Therefore, emotional items may have actually been encoded *less* strongly in patients versus controls. As with the N2 waveform, LPP amplitude within the SCZ group did not differ as a function of patients' INT or EXT symptomatology.

Interestingly, neutral LPP amplitude was significantly larger in the SCZ versus HC group. This suggests patients may have ascribed some degree of emotional significance to neutral words—an effect that has been referred to as the “affective misattribution bias” (p. 248, Holt et al., 2006). This may partly explain why patients in the current sample did not exhibit a differential DF effect for negative and neutral words. If patients' neural responses were similar for negative and neutral stimuli, they may have perceived and encoded these stimuli in a qualitatively similar way and, by extension, had equivalent difficulty selectively inhibiting and/or rehearsing TBF and TBR words, respectively, regardless of emotional valence. At a broader level, this possibility draws attention to the importance of accounting for baseline differences in the processing of neutral stimuli when investigating abnormal emotion-cognition interactions in SCZ. This argument is clearly illustrated in the literature on amygdala activation in persons with SCZ. A number of studies have reported decreased amygdala activation in response to emotional stimuli compared to HCs (e.g., Gur et al., 2002; Takahashi et al., 2004). However, research by Hall et al.

(2008) has demonstrated that the purported decrease in amygdala activation may actually result from an *increase* in baseline amygdala activation in response to neutral stimuli. These data highlight how emotion processing abnormalities in SCZ can be easily misinterpreted when the affective misattribution bias is not considered or experimentally controlled.

5.4.2.3. Selective rehearsal: The P300 waveform. At posterior sites, remember cues elicited an enhanced P300-like waveform compared to forget cues. This is consistent with multiple DF studies that have shown an enhanced positivity for remember versus forget cues with a latency range of approximately 300-400ms after cue onset (Cheng et al., 2011; Hsieh et al., 2009; Hauswald et al., 2010; Paz-Caballero et al., 2004; van Hooff & Ford, 2011; Yang et al., 2012). In the context of previous research linking the P300 to memory encoding (Azizian & Polich, 2007) and rote rehearsal (Polich, 2007), the current data offer further support for the P300 waveform as an index of selective rehearsal on the DF task. Together with the enhanced N2 following forget cues, these results suggest that the item-method DF effect is reflective of *both* goal-directed inhibition and selective rehearsal processes.

As with the N2 component, the main effect of instruction on P300 amplitude was not modulated by group. However, planned comparisons did reveal that remember cue-induced P300 amplitude was greater for cues following negative versus neutral words in the HC group only. This suggests that, at the neurophysiological level, the HC group instantiated more extensive rehearsal processes for negative versus neutral TBR words, whereas patients with SCZ did not.

This offers partial support for Hypothesis 3 in that patients exhibited abnormal ERPs during selective rehearsal of TBR negative versus neutral items relative to the control group. This also reinforces the notion that aberrant emotional DF in SCZ may involve processes other than goal-directed inhibition. Specifically, patients may have difficulty implementing targeted, strategic encoding processes (i.e., selective rehearsal) to aid subsequent memory performance for TBR emotional items. Indeed, research has shown that patients with SCZ are impaired in their ability to self-generate effective memory strategies (Iddon, McKenna, Sahakian, & Robbins, 1998) and show inefficient encoding at a neural level compared to controls (Cairo, Woodward, & Ngan, 2006). However, a caveat to the abnormal selective rehearsal account is that the observed pattern of ERP data did not translate into differential recognition performance as a function of emotion within the SCZ group. That is, the patients did not show a reduced behavioural DF effect for negative words, despite their abnormality in rehearsal-based ERP activity for TBR negative words. Finally, as with the N2 and LPP waveforms, P300 amplitude within the SCZ group did not differ as a function of patients' INT or EXT symptomatology.

5.4.3 Limitations & Future Directions

There are several potential limitations of the current study that warrant additional consideration and can be used to guide future research. First, subsequent memory effects were not examined for remember and forget cue waveforms. That is, no differentiation was made between forget cue waveforms associated with successfully forgotten (TBF-miss) versus unsuccessfully forgotten (TBF-hit) words, or

remember cue waveforms associated with successfully remembered (TBR-hit) versus unsuccessfully remembered (TBR-miss) words. At a conceptual level, it is reasonable to suggest that successful implementation of remember and forget cues would be associated with more distinct neurophysiological markers of rehearsal and inhibition, respectively. Indeed, several DF studies have used this approach and found subsequent memory effects for various different ERP components (Hsieh et al., 2009; van Hoof & Ford 2011; Wylie et al., 2008; Yang et al., 2012). Thus, it is possible that the predicted difficulty in resolving emotional and goal-directed cognitive processes in SCZ was obscured to some extent by including all cue-induced ERPs in our analyses, rather than classifying them according to subsequent recognition performance. Unfortunately, one of the difficulties in pursuing this type of analysis is obtaining enough trials within the four subsequent memory categories (i.e., TBF-miss, TBF-hit, TBR-miss, TBR-hit) to calculate reliable ERPs—a problem that is made more difficult when these categories must also be subdivided by emotion. This precluded a subsequent memory analysis in the current study, but should be accounted for methodologically in future experiments.

Second, negative and neutral words were not precisely matched for word frequency within the study list (see Table 5.2), with frequency ratings being lower for negative words ($p = .04$). This is noteworthy as frequency can influence word processing at behavioural and neurophysiological levels. Concerning the latter, low-frequency (LF) words typically elicit higher amplitude early latency ERP components, such as the N1 and P1, than high-frequency (HF) words (Hauk &

Pullvermüller, 2004). Of particular relevance to the current study, a similar pattern (i.e., LF > HF) has been found in later latency time windows (320-360ms; Hauk & Pullvermüller, 2004). Given that negative study words had lower frequency ratings in the current study, it is plausible that the GROUP x VALENCE interaction observed for LPP amplitude at posterior sites (i.e., negative > neutral for HC group only) may have partly reflected differential lexical processing between groups, independent of emotion. However, the majority of studies have observed that significant main effects of word frequency are absent after 400ms post-stimulus onset (Smith & Halgren, 1987; Sereno, 1998; Brown, Hagoort, & ter Keurs, 1999, King & Kutas, 1998; Embick, Hackl, Schaeffer, Kelepir, & Marantz, 2001). Given that the analysis window for LPP latency in the present study began at 400ms, the influence of word frequency on LPP amplitude was likely minimal.

Third, there were several instances within the current dataset in which behavioural and ERP data were in apparent dissociation. For example, the main effect of instruction on both N2 (TBF > TBR) and P300 (TBR > TBF) amplitude was not modulated by group, yet only the HC group showed a behavioural DF effect. In addition, recognition data suggests higher levels of INT psychopathology were associated with greater difficulty forgetting negative words, yet similar associations were not found for any of the ERP components. Such disagreement makes it more challenging to interpret the functional significance of the ERP effects. That said, dissociation between behavioural and ERP effects is not unprecedented in the DF literature. Using an emotional DF paradigm, Bailey and Chapman (2012) observed a

clear instruction by emotion interaction, but no moderation of the associated ERP components. The authors partly accounted for this discrepancy by suggesting that the disruptive effect of emotion on DF may have been evident during retrieval operations within the *recognition* phase. In this context, a recent item-method DF experiment found a distinct pattern of ERP activity during the recognition phase that was associated with successfully forgotten items only—i.e., the “reversed old/new effect” (p. 99, Nowicka et al., 2009). Thus, it is plausible that SCZ-related ERP abnormalities associated with reduced DF in the present study were only evident in the recognition phase. Future experiments could offer a more comprehensive electrophysiological explanation of emotional DF in SCZ by integrating ERP results from both the encoding and recognition phases.

Fourth, the current ERP dataset is limited in terms of its ability to identify the neuroanatomical substrate underlying competition between emotional memory formation and encoding suppression in SCZ. The interaction between these opposing processes is undoubtedly represented by a distributed neural network. Therefore, neuroimaging techniques capable of quantifying interregional communication will be critical for characterizing the functional neural architecture associated with emotion-cognition antagonism in SCZ. In this regard, multivariate approaches to analyzing fMRI data hold significant promise. For example, covariance techniques, such as partial least squares or dynamic causal modeling, could be employed to help delineate patterns of effective connectivity across brain regions that act in concert to support emotional DF. In turn, this may enhance our understanding of the

pathophysiology associated with abnormal integration of emotional and goal-directed cognitive processes in SCZ.

5.5 SUMMARY & CONCLUSIONS

In summary, group-level behavioural data indicate that patients with SCZ showed a general reduction in DF compared to HCs that was not modulated by emotion. However, when examined in terms of INT and EXT psychopathology, it appears that the former may be associated with greater difficulty intentionally forgetting negative information in SCZ. Our ERP data did not support the assertion that strategic inhibitory processes aimed at suppressing encoding are disrupted by opposing emotional information that promotes encoding in SCZ patients. Moreover, patients' ERP data suggest they did not exhibit disproportionately heightened encoding of emotion-laden stimuli. Rather, the most prominent ERP abnormality among patients was that, unlike HCs, they did not exhibit enhanced P300 amplitude (a putative index of selective rehearsal) for remember cues following negative stimuli. Thus, the current data tentatively suggest that diminished ability to engage targeted memory encoding strategies directed at negative items may underpin abnormal emotional DF in patients. However, further research is needed to (1) link each ERP component to subsequent memory effects, (2) examine ERP activity during the recognition phase, and (3) clarify the role of INT psychopathology in emotional DF regardless of diagnostic category.

APPENDIX A

Summary of exploratory correlational analysis between INT/EXT psychopathology and N2, P300, and LPP waveforms

	Internalizing		Externalizing	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
N2_For_Neg	-.22	.38	-.07	.77
N2_For_Neu	-.19	.44	.01	.98
P3_Rem_Neg	-.00	.99	-.11	.66
P3_Rem_Neu	-.05	.84	-.02	.93
LPP_Ant_Neg (200-400ms)	-.06	.82	-.05	.85
LPP_Ant_Neu (200-400ms)	-.18	.47	-.24	.33
LPP_Pos_Neg (200-400ms)	.48	.04	.42	.08
LPP_Pos_Neu (200-400ms)	.23	.34	.13	.60
LPP_Ant_Neg (400-600ms)	-.37	.12	-.29	.23
LPP_Ant_Neu (400-600ms)	-.31	.19	-.34	.15
LPP_Pos_Neg (400-600ms)	.07	.78	.00	.99
LPP_Pos_Neu (400-600ms)	.01	.98	-.12	.62
LPP_Ant_Neg (600-800ms)	-.51	.03	-.47	.04
LPP_Ant_Neu (600-800ms)	-.48	.04	-.47	.04
LPP_Pos_Neg (600-800ms)	-.19	.44	-.19	.44
LPP_Pos_Neu (600-800ms)	.09	.71	-.09	.72

Note: An adjusted alpha value of .01 was used to determine statistical significance. Abbreviations: INT = internalizing; EXT = externalizing; For = forget cue; Rem = remember cue; LPP = late positive potential; Ant = anterior electrode sites; Pos = posterior electrode sites; Neg = negative; Neu = neutral

ACKNOWLEDGEMENTS

This research was supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research awarded to Regan Patrick. The authors would like to thank Iulia Patriciu, Katie Herdman, Carolyn Roy, and Roshi Wagley for their contributions towards participant recruitment, data collection, and data management.

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CHAPTER 6

GENERAL DISCUSSION

6.1 SUMMARY OF RATIONALE, OBJECTIVES, AND RESULTS

Previous studies exploring emotion-cognition interactions in SCZ have focused on the impact of extraneous, task-irrelevant emotional distraction on primary cognitive processing. This body of research has produced inconsistent findings across behavioural and neural levels of analysis. Such inconsistencies highlight the need for further research to elucidate the conditions underpinning abnormal emotion-cognition interactions in SCZ. Accordingly, the primary goal of the current thesis was to further characterize the parameters under which faulty emotion-cognition interactions emerge in SCZ.

The theoretical anchor for the current research stems from an evolution-centered, dual-systems model of SCZ that emphasizes a selective deficit in goal-directed (dorsal) versus emotion-driven (ventral) brain circuits—i.e., the dorsal deficiency model (Christensen & Bilder, 2000; Giaccio, 2006). This model posits that primary impairment in dorsal brain systems (including hippocampus, PFC, and amygdala) causes deficits in goal-directed, cognitive processing, perhaps leading to untempered emotion-driven behaviour due to relative ventral system hyperactivity. A commensurate pattern of dysregulation has been observed in animal models of SCZ that also highlight impairment in key dorsal system structures. Grace's (2000, 2003) corticolimbic gating model suggests that disrupted hippocampal development results in diminished goal-directed, contextual behaviour subserved by the PFC. In turn, this leads to behaviour that is driven in an antagonistic or competitive fashion by affective inputs from the amygdala. Therefore, convergent human and animal models argue

that deficits in dorsal brain systems underpin dysregulated emotion-cognition integration in SCZ. These models further suggest that the disruptive impact of emotional stimuli may be amplified when emotional cues are actionable and signal a response that is antagonistic to task-relevant, goal-directed behaviour. This prediction, however, has not been validated in a human clinical sample. Thus, our experiments tested the central hypothesis that patients with SCZ have difficulty prioritizing goal-directed, cognitive response cues in the face of countermanding emotional cues that impel an alternative response. On balance, the current data (reviewed below) support this hypothesis.

The experiment presented in Chapter 2 (CERT/CDRT) was borne out of research that has identified prepotent motor responses elicited by emotion-laden stimuli. This research was leveraged to design a completely novel task, the CERT, which examines how motor responding is regulated when individuals are confronted with competing cues that impel a goal-directed, contextual action versus a prepotent, emotion-driven action. In contrast to our central hypothesis, results from the CERT showed that patients with SCZ did not differ from HCs in their ability to resolve this cue conflict. However, within the SCZ group, patients' ability to use contextual cues to override emotion-driven motor responses was worse compared to overriding non-emotional (direction-based) responses, indexed by a non-emotional analog task (CDRT). When patients were then subdivided according to the presence or absence of disorganized symptoms, only the former showed selective difficulty with emotional versus non-emotional response conflict. These data, therefore, offer

modest or partial support for our central hypothesis as patients exhibited selective difficulty overcoming emotional (versus non-emotional) response cues when competing, goal-relevant task demands call for such action. However, these data also suggest that certain dimensions of psychopathology (i.e., disorganized symptoms) may play a significant role in the emergence of dysregulated emotion-cognition antagonism when guiding motor responses. Additionally, this experiment supports the utility of the CERT/CDRT as a novel experimental paradigm for investigating emotion-cognition antagonism in clinical populations.

The experiment presented in Chapter 3 employed an existing social-cognitive paradigm (FVT) to examine how patients respond when confronted with competing stimuli which impel automatic versus effort emotional processing. Importantly, the task parameters and data analysis were modified from previous iterations of this task in order to (1) minimize the influence of potential confounding factors (working memory load) and (2) explore other sources of variance not accounted for in previous experiments (reading ability, basic facial emotion recognition, and IQ). Results showed that, compared to HCs, patients with SCZ relied less on cues that necessitated effortful emotional processing (vignette responses) and more on cues that elicited automatic emotional processing (face responses) when the two were placed in direct conflict. These data, therefore, support our central hypothesis that patients' responses are guided less by contextual information (effortful emotional processing) and more by prominent affective information (automatic emotional processing). Interestingly, this imbalance was moderated by estimated IQ, suggesting that

dysregulated emotion-cognition antagonism when making socio-emotional judgments may partly hinge on intellectual ability, not simply diagnostic category.

The experiment presented in Chapter 4 used an emotional DF paradigm to characterize how competing task-relevant and emotion-driven memorial cues are reconciled. This is the first study to date that has examined emotional DF in patients with SCZ and, in this way, is a novel contribution to cognitive psychopathology research. Results showed that patients with SCZ had a reduced DF effect for negative words compared to HCs and, to a lesser extent, relative to neutral and positive words. Importantly, this valence-selective reduction in DF appears to have been driven by reduced forgetting of TBF negative words, not facilitated recall of TBR negative words. This pattern of results suggests that individuals with SCZ were less able to instantiate goal-directed inhibitory mechanisms in service of overriding automatic emotional memory enhancement of negative stimuli, thereby supporting our central hypothesis. Unlike the previous two experiments, this study did not find any notable correlations between dysregulated emotion-cognition antagonism (i.e., reduced negative DF) and dimensions of psychopathology or cognitive functioning.

The experiment presented in Chapter 5 extended the emotional DF task to an ERP paradigm. This experiment is the first to examine the neurophysiological correlates of DF in patients with SCZ for either non-emotional or emotional stimuli. In this context, previous DF studies have been largely speculative in explaining the neurocognitive mechanisms associated with abnormal DF in SCZ. Such speculation is risky in light of multiple possible mechanisms that could account for abnormal DF.

Therefore, this experiment aimed to provide a more direct examination of the neurocognitive processes underpinning abnormal DF (emotional and non-emotional) in SCZ, as well as the neural dynamics associated with dysregulated emotion-cognition antagonism in these patients. Contrary to results from Chapter 4, patients with SCZ did *not* exhibit reduced DF for negative words. In addition, ERP data indicate that goal-directed inhibitory mechanisms (N2) were *not* differentially perturbed in SCZ patients when confronted with competing emotional response cues. These data, therefore, offer only limited support for our central hypothesis. Interestingly, however, exploratory correlational data suggest that difficulty forgetting negative stimuli may have been present in patients with higher levels of INT psychopathology. Correlations with N2 further suggested that greater INT symptoms may have been associated with a *general* inhibitory deficit among patients with SCZ, though this finding requires replication with larger samples. Unexpectedly, P300 data suggested that abnormal emotional DF in SCZ may represent a failure to engage targeted memory encoding strategies directed at emotional content. Clearly, further research is needed to elucidate the potentially complicated relationships between diagnosis and underlying psychopathological dimensions as they relate to ERP waveforms (in particular the N2 and P300) in SCZ.

Taken together, the current results support the assertion that deploying goal-directed cognitive processing resources in the face of competing emotional responses is disproportionately difficult for patients with SCZ, such that emotional cues signaling a particular action impart undue influence on behaviour, even under

conditions where a competing cognitive cue is given priority. More broadly, these data offer behavioural validation for the dorsal deficiency model of SCZ, which predicts an imbalance between brain systems subserving cognitive (dorsal) and emotional (ventral) processing. Indeed, two of four experiments (FVT and list-method emotional DF) clearly showed that patients with SCZ had difficulty utilizing goal-relevant cognitive cues to guide behaviour when faced with antagonistic emotional response cues. To a lesser extent, slower RTs for cue conflict trials on the CERT versus CDRT among SCZ patients (Chapter 2) also suggests selective difficulty overcoming emotional (versus non-emotional) response cues when goal-relevant task demands call for such action. Moreover, even though the item-method emotional DF task (Chapter 5) did not replicate the list-method findings from Chapter 4 at a group level, correlational data suggest that a subset of patients with higher levels of INT psychopathology may demonstrate a similar effect. Thus, each of the four studies in the current thesis provided some degree of support for our central hypothesis. Given that this pattern of data was observed across a diverse set of tasks, it is reasonable to suggest that the primary tenet of the dorsal deficiency model (embodied in our central hypothesis) offers a useful heuristic for considering dysregulated emotion-cognition antagonism across different processing domains and should be employed further in generating novel experiments to test its predictions.

6.2 DISTRACTION VERSUS DIRECT ANTAGONISM

As noted above, dorsal deficiency models suggest that the disruptive impact of emotion on primary cognitive processing in SCZ may be intensified when emotional cues are actionable and signal a response that is antagonistic to task-relevant, goal-directed behaviour. In other words, patients with SCZ may have greater difficulty overcoming direct emotional antagonism versus extraneous emotional distraction. But was this prediction supported by the current data?

Before examining how the present data can inform the validity of this prediction, it is worthwhile to briefly consider conceptual differences between antagonistic and distraction-based tasks, as well as why the former might be more problematic for patients with SCZ. One of the key discriminating features of antagonistic versus distractor tasks is the level of conflict that is elicited between the emotional and cognitive cues. On distractor tasks, emotional information might momentarily capture one's attention, though not necessarily for the purposes of enacting an alternative response. Although emotional cues likely are always *potentially* actionable and adaptive—that is *why* they capture our attention—it is in the unfolding of greater appraisal that many emotional cues are dismissed as not relevant and not in need of action. The conclusion of irrelevancy is made that much more difficult in the circumstance where a cue is *clearly* actionable and antagonistic to the cognitively determined alternative action. Thus, antagonistic tasks place emotional information in a conceptually unique role by testing the extent to which emotion-laden stimuli can effectively *guide* behaviour, rather than simply modulating or transiently disrupting ongoing behaviour. More importantly, this role of emotion

is examined in a context for which expressing emotion-driven behaviour is antithetical to goal-relevant task demands. Antagonistic tasks, therefore, can provide a robust examination of dorsal-ventral system imbalance predicted by dorsal deficiency models of SCZ.

With this context in mind, antagonistic tasks may be particularly problematic for patients because they necessitate a higher degree of effortful constraint once the conflict between emotional and cognitive cues has been consciously registered. Implementing such constraint adds another layer of goal-directed behaviour (response inhibition) on top of pre-existing cognitive task demands—both of which likely challenge an already-compromised dorsal system in SCZ. Accordingly, each of the four experiments described here provided some evidence that primary cognitive processing was disproportionately perturbed by the presence of actionable, antagonistic emotional cues, though the strength of this effect depended on the specific task that was used and possibly on certain dimensions of psychopathology. By contrast, behavioural data from a majority of previous emotional distraction studies have generally shown that, relative to controls, patients were *not* disproportionately vulnerable to perturbation by extraneous emotional distraction (see Chapter 1, Section 5). With the possible exception of patients characterized by elevated positive symptoms, SCZ groups have mostly demonstrated equivalent or reduced susceptibility to emotional distraction. It is important to note, however, that neuroimaging data derived from distraction-based tasks more consistently show abnormal patterns of brain activation in response to emotional distraction, though

this has frequently been observed in the context of null behavioural effects. Thus, from a qualitative standpoint, the present data offer tentative support for the assertion that direct antagonism *is* more problematic for patients than extraneous distraction at a behavioural level of analysis.

From a quantitative standpoint, determining whether emotional antagonism is more problematic than emotional distraction is best accomplished by directly comparing effect sizes from the current data to previous research in which patients showed increased susceptibility to emotional distraction. Although a general comparison would likely be confounded by unequal task difficulty and different outcome variables, it still provides a reasonable estimation of differential impairment, if any, on antagonism versus distraction-based tasks. In this context, effect size values in the current thesis varied considerably across studies, ranging from small (Cohen's $d = 0.09$ to 0.25) on the CERT (Chapter 2) and item-method emotional DF (Chapter 5), to moderate ($d = 0.42$ to 0.71) on the CERT-CDRT comparison (Chapter 2) and list-method emotional DF (Chapter 4), to large ($d = 0.90$ to 1.33) on the FVT (Chapter 3). Unfortunately, the few distraction-based studies that have shown increased affective interference (Bental & Kaney, 1989; Besnier et al., 2011; Epstein et al., 1999; Mohanty et al., 2008; Park et al., 2008) did not report effect sizes or the raw values necessary to compute them, precluding a direct quantitative comparison with the present data. Therefore, an important avenue of investigation for future research will be to directly compare patients' performance on antagonism versus

distraction-based tasks which use the same dependent variables and are equated for difficulty.

6.3 BROADER IMPLICATIONS OF THE CURRENT FINDINGS

The present data have more far-reaching implications beyond providing behavioural validation for dorsal deficiency models of SCZ and offering support for the assertion that emotional antagonism is more problematic than distraction. These data can inform patterns of neural network dynamics associated with dysregulated emotion-cognition antagonism. These results also have implications for SCZ psychopathology, with several findings suggesting dysregulated emotion-cognition antagonism might be associated with certain dimensions of psychopathology that cut across diagnostic boundaries, rather than just SCZ. These data also have potentially meaningful treatment implications, particularly with respect to current approaches to psychological intervention. In addition, several inconsistent and null findings highlight the need for further research in order to refine the meaning and implications of these results. Each of these discussion points is addressed in greater detail in the following sections.

6.3.1 Implications for Neural Network Dynamics

Dual-system models of emotion-cognition interaction posit that goal-directed, cognitive (i.e., top-down) and stimulus-driven, emotional (i.e., bottom-up) processing streams operate in concert to generate the most adaptive behaviour in a given situation (e.g., Epstein, 2010; Grace, 2003; Kahneman, 2003; Metcalfe & Mischel,

1999; Speechley & Ngan, 2008). On the one hand, a critical function of the cognitive system is to provide top-down modulation of emotional behaviour by prioritizing goal-relevant stimuli and suppressing competition from emotion-laden response cues. On the other hand, a central function of the emotional system is to provide bottom-up, stimulus-driven redirection of information processing resources towards motivationally significant stimuli in the external environment. In this way, emotion can either enhance or disrupt cognitive processing in order to manage the immediate, affectively-charged situational demands (Gray, 2001; Gray, Braver, & Raichle, 2002). Inherent within this bi-directional flow of information is an element of competition between the two systems which requires situationally-appropriate resolution for adaptive functioning. This begs the question of whether abnormal emotion-cognition antagonism observed within the current SCZ sample reflects (1) aberrant top-down modulation by goal-directed, cognitive brain circuits or (2) dysfunctional bottom-up modulation by stimulus-driven, emotional circuits. Although the dorsal deficiency model would argue the former, and several current findings support this assertion, the present data, on whole, are somewhat agnostic with regard to this question; that is, the studies varied in the extent to which the separate contributions of cognitive tempering versus affective amplitude could be reliably estimated.

Results from Chapter 5 (emotional DFT + ERP) hold particular relevance in understanding the neural dynamics of emotion-cognition antagonism in SCZ as these are the only data derived from a functional neuroimaging paradigm. ERP data indicate that patients with SCZ did *not* differ from healthy individuals in their

capacity to instantiate strategic cognitive resources (inhibition) to overcome emotional cue conflict. Rather, these data suggest patients may have failed to utilize bottom-up, emotion-driven processing to facilitate goal-directed cognitive responding. Specifically, *only* HCs exhibited larger P300 amplitude for remember cues that followed negative versus neutral words. The P3b subcomponent of the P300 is a reliable index of selective rehearsal and encoding that is generated within frontal and temporoparietal regions (Polich, 2010). Therefore, absence of P300 amplitude change in response to negative remember cues among SCZ patients suggests emotion did not enhance goal-relevant encoding processes. This same lack of facilitation was observed in the list-method emotional DF task in Chapter 4 in both patient and control groups.

In terms of underlying neuroanatomy, it is well established that amygdala activity facilitates hippocampal-dependent memory encoding, thereby giving rise to automatic emotional memory enhancement (LeBar & Cabeza, 2006; Phelps, 2004; Dere et al., 2010). For example, impaired memory for emotional stimuli has been linked to a decrease in functional connectivity between the amygdala and hippocampus (Dere et al., 2010). Unmodulated P300 amplitude in response to negative remember cues, therefore, suggests that a critical region within the stimulus-driven, emotional neural system (amygdala) may have failed to boost activity within the goal-oriented, memory formation system (hippocampus) in patients with SCZ. In other words, patients with SCZ may have exhibited dysfunctional bottom-up modulation of goal-directed cognitive processing.

Alternatively, patients with SCZ may not have sufficiently differentiated between negative and neutral words, perhaps leading to inappropriately heightened activity within emotional circuits in response to neutral words. In this case, we would not expect remember-cue P300 amplitude to be differentially modulated by negative versus neutral content, as was observed. In support of this explanation, patients demonstrated abnormally increased LPP amplitude in response to neutral words, suggesting they perceived some degree of emotional significance in the neutral items. This aligns with the aberrant salience/affective misattribution models of SCZ (Holt et al., 2006; Kapur, 2003), both of which posit that ineffective top-down modulation of emotional circuits may contribute to such abnormal emotional percepts.

Consistent with this assertion, several current findings suggest diminished top-down modulation of emotion-driven neural circuits. Patients with SCZ had a reduced DF effect for negative content that resulted from reduced forgetting of TBF negative items (Chapter 4). This suggests an impaired ability to engage strategic inhibitory mechanisms in service of overriding bottom-up, automatic emotional memory enhancement. Neuroanatomically, several lines of evidence implicate a broad frontal control network in emotional memory inhibition (e.g., Depue, Banich, & Curran, 2007; Nowicka et al., 2011). For example, using a cognitive paradigm specifically designed to elicit emotional memory suppression (i.e., emotional think/no-think task; TNT), Depue and colleagues (2007) observed that increased recruitment of the DLPFC was associated with concomitant reduction in bilateral hippocampal activity, which predicted successful memory inhibition. They also reported down-regulation

of amygdala activity associated with successful inhibition of memory for emotional stimuli. This suggests that prefrontal mechanisms responsible for memory inhibition down-regulated neural regions involved in emotional memory formation, rendering the unwanted emotional memory more difficult to retrieve. Thus, it is plausible that reduced emotional DF reflected diminished top-down modulation of emotion-driven responding by goal-directed prefrontal circuits in SCZ. This supposition aligns with dorsal deficiency models of SCZ that predict such dysregulation when emotional and cognitive cues oppose one another (Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003).

Results from Chapter 3 (FVT) further suggest diminished top-down modulation of emotion-driven neural circuits. Patients relied significantly less on deliberative, effortful emotion processing (i.e., reduced vignette responding) and more on automatic emotional processing (i.e., increased face responding) when responding to conflicting socio-emotional information, though this pattern was moderated by IQ. Previous research suggests the effortful and automatic emotional processes elicited by this task (situational context and facial emotion processing, respectively) map onto the dorsal-ventral functional dichotomy described above (Phillips, Drevets, Rauch, & Lane, 2003). There is an extensive literature highlighting the role of the amygdala (ventral) in facial emotion processing (see meta-analyses by Fusar-Poli, Placentino, Carletti, Landi, Allen, et al., 2009; Sabatinelli, Fortune, Li, Siddiqui, Krafft et al., 2011). Moreover, there is considerable data implicating prefrontal and hippocampally-centered networks (dorsal) in both context processing

(Hayes, Baena, Truong & Cabeza, 2009; MacDonald & Carter, 2003; Smith & Mizumori, 2006; Winocur & Gilbert, 1984) and various aspects of linguistic processing (Awad, Warren, Scott, Turkheimer, & Wise, 2007; Yarkoni, Speer, & Zacks, 2008; Duff & Brown-Schmidt, 2012; Noppeney, Price, Duncan, & Keopp, 2005)¹⁵. Thus, patients' behavioural response pattern on the FVT suggests diminished dorsal network activity, perhaps resulting in inappropriately amplified or untempered ventral network activity relative to HCs.

It is important to highlight, however, that the aforementioned patterns of data do not conclusively inform whether dysfunction in one network mediated abnormalities in the other and, if so, which direction this mediational effect was operating. For instance, it is plausible that heightened activity within emotion-driven circuits actually suppressed activation in goal-directed, cognitive circuits, thereby generating the imbalances observed on the FVT and list-method emotional DF task. The current data, therefore, do not reveal a definitive pattern regarding the direction of emotion-cognition dysregulation in SCZ. Elucidating such patterns will ultimately require functional neuroimaging techniques that permit a finer-grained assessment of coordinated neural activity along pre-specified pathways. In this vein, dynamic causal modeling (DCM; Friston et al, 2003) is a hypothesis-driven approach to analyzing effective connectivity¹⁶ among distributed regions within a circumscribed

¹⁵ Although the emotional content of the vignettes might also elicit amygdala activation, empirical data in this regard are equivocal (Ferstl, Rinck, & von Cramon, 2005; Ferstl & von Cramon, 2007).

¹⁶ Effective connectivity is defined as the influence that one neural system exerts over another via direct or indirect neuronal pathways.

neural network. While traditional fMRI analysis methods (e.g., subtractive methods that typify software such as Statistical Parametric Mapping or Brain Voyager) primarily generate descriptive representations of *differences* in brain activity, DCM models causal relationships between pre-determined regions as they relate to experimental manipulations of interest (Sladky et al., 2013). Importantly, within these models the direction of the relationship is, *de facto*, specified and constrained, thereby permitting analysis of effective connectivity based on known anatomy and physiology. Thus, future research could examine multiple possible models of abnormal prefrontal-limbic network activity to better characterize the neural dynamics associated with dysregulated emotion-cognition antagonism in patients with SCZ.

Any such network-level predictions must be constrained by known patterns of structural connectivity within the goal-directed (dorsal) and emotion-driven (ventral) neural circuits. Human and non-human primate research provides insight into such connectivity patterns. In general, this research indicates that DLPFC and DMPFC have minimal direct projections to the amygdala. Rather, the largest frontal output to the amygdala arises from subgenual (BA25) and dorsal (BA32) ACC (Ray & Zald, 2012). Contrary to some functional connectivity data (e.g., Anticevic et al., 2012b), this pattern of structural connectivity suggests that any influence on limbic activity by dorsal PFC is indirect, perhaps through medial prefrontal structures such as subgenual and dorsal ACC. Indeed, dorsal ACC receives substantial projections from DLPFC and DMPFC, and, in turn, has well-delineated projections to the amygdala

(Ray & Zald, 2012). With this in mind, diminished top-down modulation of emotion-driven responding on the FVT (Chapter 3) and emotional DFT (Chapter 4) in SCZ patients may not have resulted from direct regulation of limbic activity by dorsal prefrontal regions. Rather, this may have occurred through a relay structure that is more closely integrated with emotional brain circuits. This possibility illustrates the importance of anchoring predictions of neural network dysfunction in SCZ within empirically-derived theories of functional neuroanatomy *and* known patterns of structural connectivity.

6.3.2 Implications for Psychopathology

The current data suggest that dysregulated emotion-cognition antagonism may provide a useful framework for explaining certain dimensions of SCZ psychopathology. Results from Chapters 3 and 4 (and to a lesser extent Chapter 2) indicate patients with SCZ may have disproportionate difficulty resolving competition between goal-relevant and emotion-driven response cues. Specifically, their actions may reflect diminished goal-directed regulation of emotion-driven behaviour. This assertion has similarities with the aberrant salience (Kapur, 2003) and affective misattribution (Holt et al., 2006) hypotheses, which posit that delusional ideation may stem from dysfunctional top-down modulation of abnormal emotional percepts. It is plausible, therefore, that impaired conflict resolution between emotional and cognitive response determinants may contribute to the formation and maintenance of delusions in SCZ.

In this context, Speechley and Ngan's (2008) model of reasoning provides a possible explanation for delusion formation in SCZ that is grounded in a dual-system framework. They motivate their study from the intuition versus reasoning framework of Tversky and Kahneman (1974), which specifies that reasoning is governed by interactions between a "fast, intuitive, and automatic" stream (Stream 1) and a "slow, conscious, and deliberative" stream (Stream 2) (p. 1210; Speechley & Ngan, 2008). According to Speechley and Ngan, emotional stimuli initially bias decision making towards Stream 1; however, should conflict arise between the two streams, healthy individuals will typically recruit Stream 2 in order to "initiate a more thorough consideration of all available evidence" (p. 1212). This implies that Stream 2 can implement corrective modifications when behaviour is erroneously based on Stream 1. In SCZ, Speechley and Ngan argue that delusions may arise from dysregulated integration of Stream 1 and 2 processing—the dual stream modulation failure (DSMF) hypothesis. According to this hypothesis, dysregulation can result from two possible mechanisms which may occur in tandem or separately: conflict modulation failure (CMF) and/or accentuated emotional modulation (AEM). In CMF, Stream 2 is no longer preferentially recruited during periods of conflict, thereby diminishing the influence of contradictory evidence and "increasing the likelihood that Stream 1 endorsed beliefs will endure uncorrected" (Speechley, Woodward, & Ngan, 2013). On the other hand, AEM predicts that heightened emotional states may amplify patients' bias towards Stream 1 processing and "further diminish the potentially corrective influence of Stream 2" (Speechley et al., 2012).

Thus, when conflicts involving emotional material arise, individuals with SCZ may exhibit a breakdown in contextual, goal-focused regulation of inputs to decision-making, thereby grounding decisions in emotion rather than logic. This prediction closely aligns with the tenets put for by dorsal deficiency models of SCZ (Christensen & Bilder, 2000; Giaccio, 2006; Grace, 2003).

Support for CMF in SCZ has been reported in deductive reasoning studies using conflict and non-conflict conditional statements (Speechley, Murray, McKay, Munz, & Ngan; 2009; Speechley et al., 2013). Relative to HCs, delusional SCZ patients exhibited a disproportionate deficit on conflict trials in which there was disagreement between the logical validity and semantic believability of a premise and conclusion. Moreover, patients had significantly reduced BOLD signal within a dorsally-mediated neural network associated with deliberative reasoning (DLPFC) and conflict processing (dACC) compared to HCs on conflict trials (Speechley et al., 2013). However, further performance decrements were not observed at a behavioural or neural level in the SCZ group on emotion-laden conflict trials, making the impact of AEM less clear. The authors speculated that this null effect may have been due to emotional stimuli having limited personal relevance, thereby generating insufficient arousal. Nevertheless, the DSMF model and associated data are broadly consistent with the idea that delusions may be borne out of difficulty regulating competition between goal-relevant and emotion-driven responding.

An important caveat in linking delusion formation with abnormal emotion-cognition antagonism is that none of the current experiments revealed a statistical

correlation between delusional ideation and experimental task performance in patients with SCZ. Although a link with delusion formation is interesting at a conceptual level and warrants further investigation, it remains empirically unsupported based on the current dataset. On the other hand, the present data more directly relate other dimensions of psychopathology with dysregulated emotion-cognition antagonism. Specifically, disorganized (DIS) symptoms (CERT/CDRT), IQ (FVT), and INT psychopathology (emotional DF + ERP) were each associated, to some extent, with a deficiency in deploying goal-relevant cognitive processes to override emotion-driven responding.

Patients who exhibited DIS symptoms had greater difficulty utilizing contextual cues in order to inhibit competing emotional (CERT) versus non-emotional (CDRT) motor responses. Patients with lower IQ showed a similar pattern of behaviour on another task in that, compared to controls, their socio-emotional judgments hinged less on contextual cues (vignettes; effortful emotional processing) and more on salient affective cues (emotional faces; automatic emotional processing) when these cues were placed in direct conflict (FVT). The qualitatively similar impact of DIS symptoms and low IQ is consistent with previous research showing a strong correlation between these two dimensions (O'Leary et al., 2000). Moreover, such consistency indicates that both DIS symptoms and low IQ might be associated with a common deficit that disrupts patients' ability to reconcile antagonistic contextual and emotional response cues. The nature of these two tasks suggests that this common deficit is impairment in resolving response conflict.

Response conflict in this context specifically refers to situations in which habitual or prepotent responding must be inhibited in order to execute a different response (Kerns, 2009). This definition is applicable to the FVT and CERT as both tasks measured patients' ability to suppress an automatic, emotion-driven response in favour of an alternative contextual response. With this in mind, previous research has consistently shown that both DIS symptoms and lower IQ are associated with poorer performance on tasks involving prepotent or habitual response conflict, including the Stroop and A-X Continuous Performance Test (Kerns, 2009; Puccioni & Vallesi, 2012; Yücel et al., 2012). Accordingly, patients with DIS symptoms and lower IQ may be more susceptible to acting on antagonistic emotional cues by impairing patients' general ability to resolve response conflict.

Patients with higher INT symptomatology had greater difficulty overriding negative word encoding in accordance with emotional DF task demands¹⁷. This is in line with other emotional DF studies using clinical samples characterized by high INT (e.g., Domes et al., 2006; Power et al., 2000; Zwissler et al., 2012), and suggests that emotion-laden information may be particularly disruptive in SCZ patients whose clinical presentation is characterized by marked depressed mood, anxiety, fear, self-doubt, and social withdrawal. This possibility begs the question of *why* INT symptoms might be associated with dysregulated emotion-cognition antagonism in patients with SCZ. Data from a recent meta-analysis may provide some insight in

¹⁷ Preliminary neurophysiological data, however, suggest that INT may be associated with more general inhibitory deficits, though the reliability of this effect is questionable in light of the modest correlation strength and relatively small sample size.

this regard. Aldao and colleagues (2010) found that top-down emotion regulation strategies, such as reappraisal and problem solving, correlated negatively with INT symptoms. This analysis also showed that maladaptive emotion-centered strategies, such as rumination (i.e., repetitively focusing on the experiences, causes, and consequences of emotion) were more prominent in INT disorders (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Thus, to use the language of Metcalfe & Mischel (1999), individuals with higher INT psychopathology might be less able to instantiate “cool” cognitive strategies and, instead, are more likely to use “hot” emotion-focused strategies when regulating affect-driven thought and behaviour. This pattern of regulation has clear parallels with the imbalance predicted by dorsal deficiency models of SCZ. It is plausible, therefore, that the presence of *both* SCZ and INT symptoms produced an additive effect which increased vulnerability to the antagonistic pull of salient emotional response cues.

Although the data concerning INT, DIS, and IQ provide a more nuanced account of emotion-cognition dysregulation in SCZ, they do not inform whether such dysregulation is a cause or consequence of either symptom dimension. That is, it remains unclear whether these symptoms confer greater vulnerability to dysregulated emotion-cognition antagonism in SCZ *or* whether they are the clinical manifestation of chronic dual-system imbalance. A number of experimental approaches could provide clarity in this regard. For example, a within-subjects protocol could be employed whereby patients who report minimal INT symptomatology at baseline complete an emotion-cognition competition task under both normal conditions and

immediately following some form of emotion-induction that elicits an INT state (e.g., low mood, anxiety). In doing so, the contribution of INT symptoms towards dysregulated emotion-cognition antagonism could be quantified on the basis of performance changes across the two conditions. Should performance worsen in the emotion-induction condition, one might surmise that the presence of INT psychopathology renders patients more susceptible to the type of emotion-cognition dysinteraction hypothesized in the current thesis. Alternatively, patients' baseline performance on the experimental task could be used to predict the extent to which emotion induction successfully elicits an INT state. This could help determine the influence of pre-existing dual-system dysregulation on susceptibility to INT symptom formation. In this vein, structural equation modeling (SEM) may be particularly useful in delineating the causal relationship between levels of dysregulated antagonism and the symptom dimension in question.

The above discussion raises a related issue concerning whether emotion-cognition dysregulation is a core feature of SCZ or a manifestation of certain dimensions of psychopathology that are expressed more prominently within a subset of patients. The current data are largely speculative in this regard as a consistent pattern did not emerge across studies regarding which dimension(s) of psychopathology correlated with dysregulated emotion-cognition antagonism in SCZ. This issue could be clarified by leveraging the clinical heterogeneity common among SCZ samples and adopting a mixed categorical-dimensional approach. Specifically, patients who meet diagnostic criteria for SCZ could be stratified into

subgroups based on the presence of certain dimensions of psychopathology (e.g., INT and DIS symptoms). These groups could be further subdivided according to high and low levels of severity on each dimension (e.g., using a median split) and then compared on tasks that place emotional and goal-relevant response cues in opposition. Alternatively, the full range of values on each symptom dimension could be retained and examined as continuous moderator variables in relation to task performance—akin to our analysis of IQ and reading ability on the FVT. In either approach, if equal impairment is observed across patients with variable levels of the dimension in question, it would suggest that emotion-cognition dysregulation might be a core feature of SCZ. By contrast, if deficits in resolving emotion-cognition competition are more strongly related to high or low levels of a certain symptom dimension compared to the actual diagnosis of SCZ, this might suggest a specific clinical phenotype within SCZ that is linked to a particular type of psychological dysfunction—i.e., dysregulated dual-system antagonism.

The latter possibility highlights a broader issue concerning the diagnostic specificity of dysregulated emotion-cognition antagonism. If difficulty reconciling such cue conflict is more strongly related to a specific phenotype than the diagnosis of SCZ, it is possible that dysregulated emotion-cognition antagonism might be present in any individual who embodies that phenotype. This is particularly relevant for two of the dimensions observed in the current thesis—high INT symptoms and low IQ—as neither of these are specific to SCZ. Therefore, an important extension of

this research will be to investigate the impact of these dimensions on emotion-cognition antagonism across different diagnostic categories.

6.3.3 Implications for Treatment

The preceding sections collectively suggest that psychological treatment of SCZ may be particularly beneficial if the primary goal is to facilitate more deliberative, goal-relevant cognitive processing during emotionally-charged situations. This is not a novel therapeutic premise as a cardinal aspect of cognitive-behavioural therapy (CBT) for psychosis is the systematic examination of evidence that either substantiates or invalidates one's dysfunctional beliefs. In theory, engaging in this process should promote a rational analysis or reappraisal of one's faulty belief system by ensuring that only objective data—i.e., information that is not contaminated by judgments and interpretations—is considered during the evidence gathering process. In doing so, maladaptive information processing biases (e.g., emotional reasoning or catastrophizing) are attenuated, thereby weakening the cognitive foundation of psychosis. By extension, this should also reduce the emotional distress and dysfunctional behaviour that often accompanies flawed beliefs and interpretations about oneself, other people, and world.

Although the conceptual basis of CBT for psychosis is sound, empirical support for its efficacy in ameliorating symptoms is less clear. On one hand, a series of meta-analyses and empirical reviews indicate that CBT reduces positive and negative symptoms, mood, social anxiety, hospital duration, and readmissions (NICE, 2009; Rector & Beck, 2012; Wykes, Steel, Everitt, & Tarrier, 2008;

Zimmerman, Favrod, Trieu, & Pomini, 2005). These data have partly contributed to CBT being endorsed by several prominent healthcare organizations, such as the American Psychiatric Association (Lehman et al., 2004), the UK's National Institute for Health and Care Excellence (NICE, 2009), and the US Schizophrenia Patient Outcomes Research Team (Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2009). However, it has recently been suggested that the degree of therapeutic optimism surrounding CBT may be overstated. The most recent meta-analysis of CBT for psychosis, which better accounted for multiple sources of potential bias (e.g., masking, inadequate randomization, and incompleteness of outcome data) found pooled effect sizes of -0.33 for overall symptoms, -0.25 for positive symptoms, and -0.13 for negative symptoms (Jauhar et al., 2014). Importantly, effect sizes were substantially reduced after statistically accounting for masking effects. These data indicate that, while CBT can reduce SCZ symptomatology, the therapeutic effect is likely quite small.

The current thesis may provide insight into why CBT is not more effective for SCZ, as well as possible modifications that could enhance its therapeutic value. As noted above, the primary focus of CBT for psychosis is evaluating and challenging the *content* of faulty cognitions and beliefs—it does not actively target the *emotional responses* generated by these thought patterns. From a dual trends perspective, this approach represents an attempt to re-establish dorsal-ventral balance by having patients engage in a deliberative and logical analysis of their own thought content—i.e., putatively promoting activity within the hypoactive dorsal system. However, the

persistence of delusional or paranoid thought content (evidenced by the small effect size on positive symptoms noted by Jauhar et al., 2014) is a strong indication that primarily targeting reappraisal and logic is ineffective.

As indicated by much of the present data, the dorsal system is compromised in patients with SCZ, likely from pathology that is of neurodevelopmental origin. Therefore, trying to promote and leverage normal operations in a system that has never had normal structural or functional integrity may be an exercise in futility. Further complicating this approach is the potentially disruptive impact of aberrant emotional responsivity stemming from the intact, albeit *relatively* hyperactive, ventral system. With this in mind, an alternative approach to re-establishing balance between dorsal and ventral systems might be to actively target the *emotional responses* generated by dysfunctional thought patterns—i.e., tempering activity in the relatively hyperactive ventral system. The rationale for this approach has been clearly articulated by Kapur (2003) in the context of how antipsychotic medications alleviate psychotic symptoms. Kapur argues that dopamine receptor blockade leads to “dampening salience,” whereby the emotional arousal and distress tied to abnormal ideas or percepts become attenuated. This emotional dampening does not directly change the core content of one’s psychosis, but it does lessen the degree to which this content distresses the patient and drives their actions. In doing so, patients are better positioned psychologically to deconstruct and evaluate the content of their psychosis, ultimately leading to symptom remission. From this, it stands to reason that the efficacy of CBT for SCZ could be bolstered by introducing complementary

techniques that reduce emotional responsivity and distress associated with faulty beliefs (Tai & Turkington, 2009).

One of the most widely adopted and empirically validated approaches in this regard is mindfulness. Although many variations have been developed, the general goal of mindfulness-based interventions is to promote heightened awareness, acceptance, non-reactivity, and non-judgment of one's in-the-moment thoughts, feelings, physical sensations, and surroundings (Khoury, Lecomte, Gaudiano, & Paquin, 2013). That is, mindfulness-based practices promote a state of contemplation by enhancing self-directed attention, as well as shifting one's moment-by-moment experience from one of reactivity (and perhaps distress) to one of reflection and acceptance (Bishop et al., 2004). This contemplative state is cultivated by engaging in frequent mindfulness meditation exercises in which patients are instructed focus their attention on physical and emotional reactions that emerge in response to distressing thoughts and situations. A recent meta-analysis of mindfulness-based intervention for psychosis indicates small-to-moderate efficacy in treating negative and positive symptoms, though it was not clear from these results whether emotional reactivity and distress associated with these symptoms were also reduced (Khoury et al., 2013).

Functional imaging data suggest that mindfulness alters neural activity within dorsal-ventral brain circuits. For example, Herwig and colleagues (2010) observed that directing attention towards one's current emotional experience and associated bodily sensations reduces amygdala activity and increases frontal activity in areas such as DMPFC and ACC in healthy volunteers (Herwig, Kaffenberger, & Jäncke,

2010). A follow-up study (also in healthy volunteers) investigating neural correlates of brief mindfulness induction when expecting emotionally negative events found “marked recruitment of brain structures involved in top-down emotion regulation” (e.g., DMPFC; p. 8, Lutz et al., 2013). Moreover, during perception of negative stimuli, brief mindfulness induction attenuated activity in regions commonly associated with emotional responding, including the right amygdala, parahippocampal area, and insula.

Holzel and colleagues (2013) examined functional connectivity changes following a course of either mindfulness-based stress reduction (MBSR) or stress management education (SME) in patients with generalized anxiety disorder (GAD). They found increases in connectivity between the amygdala and several prefrontal regions (DLPFC, DMPFC, and dorsal ACC) after MBSR, but not after SME. In addition, the strength of amygdala-frontal coupling correlated negatively with anxiety symptom severity at post-intervention (Holzel et al., 2013). Interestingly, functional coupling changed from a negative to positive correlation after MBSR across each amygdala-frontal cluster in patients with GAD. This is notable as emotion regulation studies typically yield negative correlations, which are thought to represent increased prefrontal activity causing down-regulation of amygdala activity. The authors speculated that positive amygdala-frontal connectivity associated with MBSR may have represented “engagement in active monitoring of emotional arousal, rather than an attempt to down-regulate the emotional response” (p. 456).

Collectively, these neuroimaging data suggest that mindfulness-based interventions may work by modulating neural activity within a network of regions putatively associated with dysregulated emotion-cognition antagonism in SCZ. Therefore, incorporating mindfulness into standard cognitive-behavioural approaches may bolster the latter's therapeutic efficacy by attenuating the aversiveness of emotional reactivity. In doing so, patients may be able to more effectively interrogate and restructure their distorted belief system.

6.4 LIMITATIONS & FUTURE DIRECTIONS

There are several limitations of the current thesis that are applicable to each experiment and can be used to guide future research. First, each study utilized standardized emotional stimuli. In doing so, individual differences in how emotional stimuli were perceived were not taken into account. It is highly unlikely that the emotional content within each study had a uniform impact on all patients. This is an important consideration as personally relevant emotional information may have a greater influence on cognitive processing. For example, recent ERP data in healthy volunteers indicate that cortical processing (i.e., LPP and N400) is facilitated for unpleasant nouns only when they are preceded by a personal pronoun ("my") and not an article ("the"). Unpleasant personal nouns also had a significant memory advantage at subsequent recall (Herbert, Pauli, & Herbert, 2011). There is some evidence to suggest that patients with SCZ also process self-referential emotional information differently. For example, patients with persecutory delusions display

increased response latency for paranoia or threat-related words (Bentall & Kaney, 1989; Fear, Sharp, & Healy, 1996) and facial expressions (i.e., angry faces; Green, Williams, & Davidson, 2001). This indicates an attentional bias for emotion-laden information that is closely related to the content of their faulty belief system.

It is plausible, therefore, that patients in the current sample who perceived emotional content as personally meaningful may have been more susceptible to acting on that information at the expense of more goal-directed, task-relevant behaviour. By presenting standardized emotional stimuli to all patients, the current studies would not have captured such individual variation and may have masked the predicted effects when analyzing group-level data. Indeed, this may partly explain the variability in effect sizes obtained across studies. Future research could account for the self-referential confound by having patients rate the emotional stimuli according to personal relevance, then statistically examining these ratings as a moderating variable. Alternatively, these ratings could be used to dichotomize stimuli into personally relevant and non-relevant categories, which could then be used as a within-subjects condition in a factorial ANOVA. Either approach would permit a finer grained analysis of the role of self-referential emotional processing towards dysregulated emotion-cognition antagonism in SCZ.

A second limitation concerns antipsychotic medication effects. In each study, the SCZ group was prescribed an assortment of typical and atypical antipsychotics, and it was not possible to perform sufficiently powered statistical analyses to detect drug-specific effects. Consequently, it is unclear to what extent antipsychotic effects

impacted the present data. This limitation is not specific to the present set of experiments and poses a unique challenge to most SCZ studies. Nevertheless, it is particularly noteworthy for the current thesis in light of research showing that antipsychotics can influence emotional processing.

As noted above, Kapur (2003) argues that antipsychotics dampen the emotional salience of distressing ideas and percepts by attenuating dopaminergic drive. In this context, antipsychotics have been linked to reduced facial expressiveness, decreased experience of unpleasant emotions, and attenuated physiologic arousal in response to emotion-induction (Fakra et al., 2008; Schneider et al., 1992; see Kring & Earnst, 1999 for contrasting results). Subjective patient reports corroborate these empirical data. A recent survey of psychotic and non-psychotic psychiatric patients found that antipsychotic medications were associated with impoverished emotional range, increased feelings of indifference, and a general dampening of emotional experience (Moritz, Andreou, Klingberg, Thoering, & Peters, 2013). Similar results have been reported in a content analysis of internet comments written by patients who have taken antipsychotics (Moncrieff & Cohen, 2009), as well as case reports and experimental trials in healthy volunteers (Belmaker & Wald, 1977; Saeedi, Remington, & Christensen, 2006). These data collectively suggest that antipsychotic medications may be associated with a generally subdued emotional state. Given that all patients within the current sample were taking at least one antipsychotic, it is possible they were not sufficiently antagonized by emotional stimuli in each task. This would have weakened the intended competition between

emotional and cognitive response cues, perhaps contributing to some of the modest effect sizes and null findings.

The impact of antipsychotic medications can be clarified in several ways. Potential medication effects could be completely eliminated by running the experiments with a neuroleptic naïve sample. This might include very early first-episode patients who have yet to be exposed to antipsychotic treatment or unmedicated patients who have spontaneously stopped taking their medication. While such a sample would be ideal, there are considerable practical challenges associated with recruiting and testing neuroleptic naïve patients. An alternative approach could involve testing individuals with schizotypal personality disorder (SPD) or individuals who score high on schizotypal personality traits. Individuals with SPD (and high trait schizotypy) exhibit clinical and cognitive characteristics similar to patients with SCZ (Raine, 2006) without many of the potential confounds, including chronic neuroleptic treatment (Wilson, Christensen, King, & Zelazo, 2008). Therefore, studying these individuals may help disentangle SCZ-related abnormalities in emotion-cognition interactions from those driven solely by medication effects. A third approach might involve administering a single oral dose of antipsychotic medication to healthy volunteers and comparing subsequent performance to their normal baseline. This would provide a clearer account of pure medication effects in the absence of variance related to an underlying psychiatric disease process.

A third limitation of the present thesis concerns the sex ratio within the SCZ groups. With the exception of Chapter 5 (emotional DF + ERP), SCZ groups in each experiment had a high male-to-female ratio¹⁸. Having an unequal sex ratio is potentially problematic given the well-documented sex differences in certain aspects of emotional processing. In response to unpleasant stimuli, women tend to report greater subjective arousal, display a larger startle response, and have increased emotional modulation of the startle response compared to men (Bianchin & Angrilli, 2012; Bradley, Codispoti, Sabatinelli, & Lang, 2001; Codispoti, Surcinelli, & Baldaro, 2008). A recent meta-analysis also shows greater activation in left amygdala, left thalamus, hypothalamus, mammillary bodies, left caudate, and medial prefrontal cortex for women in response to emotionally negative stimuli (Stevens & Hamann, 2012). Neuroimaging data further show that women and men have different patterns of neuronal activation on tasks which necessitate cognitive control of emotion. Koch et al. (2007) observed that, in women, the interaction between negative emotion induction and working memory was associated with relative hyperactivation in regions associated with emotional processing, such as the amygdala and OFC. These data collectively suggest that women may have a “biologically grounded greater sensitivity and vulnerability to adverse/stressful events” (p. 925, Bianchin & Angrilli, 2012). Therefore, the relative lack of female SCZ patients in the current thesis may have resulted in smaller group-level emotional

¹⁸ This was not intentional and was simply a reflection of volunteer patterns during patient recruitment.

reactivity, thereby diminishing the strength of emotion-cognition antagonism invoked by each task. As with medication effects, this could have contributed to the generally modest effect sizes observed across studies.

A fourth limitation of the current thesis is that measures of functional outcome were not included in any of the experiments. Including such measures would have allowed us to better elucidate the functional consequences associated with dysregulated emotion-cognition antagonism in SCZ. This is a worthwhile aim for future research given the potentially significant implications of the current data for functional remediation strategies. For instance, reduced goal-directed behaviour in the face of competing emotional information suggests remediation efforts will be hindered if they immediately submit patients to environments that are highly stressful and likely to provoke emotional reactivity. Instead, a behaviourally graded approach may be more successful. That is, re-integrating patients into vocational, social, or educational settings should begin in low-stress, low-conflict, routinized environments. This could be followed by a very gradual transition to more demanding roles, allowing patients to slowly acclimate to potentially more stressful and emotionally arousing environments. Such an approach might reduce the likelihood that cognitive processing resources are hijacked or supplanted by task-irrelevant emotional features in the external environment, thereby facilitating the acquisition of skills required to optimize functional outcome.

6.5 CONCLUSIONS

The current thesis is the first attempt to systematically explore how patients reconcile competition between emotional and cognitive determinants of behaviour when they are pitted against one another, in an explicitly antagonistic fashion. The rationale for this pursuit was grounded in dual-system neurobiological models of SCZ which posit diminished influence of goal-oriented, cognitive brain circuits when faced with response cues that concurrently activate emotion-driven, reactive circuits. Results suggest that patients with SCZ may have difficulty deploying goal-directed cognitive processing resources when faced with antagonistic emotional response cues, perhaps leading to behaviour that disproportionately reflects the latter. However, the current data are not definitive in this regard as effect sizes were variable across tasks. Further research is needed to define the specific parameters under which patients with SCZ experience dysregulated emotion-cognition antagonism. In this context, these studies suggest several new avenues of investigation to help elucidate this aspect of SCZ pathology. Therefore, the current thesis is appropriately viewed as the first phase of a broader programme of research aimed at explicating the psychological and neural processes associated with SCZ-related abnormalities in regulating emotion-cognition antagonism.

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