The Nature and Specificity of Verbal Memory Interference in First Episode Schizophrenia

by

Vanessa G. DeFreitas

M.A. (Clinical Psychology), Simon Fraser University, 2005
B.Sc. (Hons.), St. Francis Xavier University, 2001

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Name: **Vanessa G. DeFreitas**

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Examining Committee: **Chair:** Dr. Rebecca Cobb
Associate Professor

Dr. Allen Thornton
Senior Supervisor
Associate Professor _____

Dr. Mario Liotti
Supervisor
Professor _____

Dr. Ivan Torres
Supervisor
Clinical Associate Professor _____

Dr. Daniel Bernstein
Supervisor
Adjunct Professor _____

Dr. Maureen Hoskyn
Internal Examiner
Associate Professor
Faculty of Education _____

Dr. Colleen Brenner
External Examiner
Assistant Professor
Department of Psychology
University of British Columbia _____

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Abstract

Chronic schizophrenia patients exhibit attenuated release from proactive interference and increased build-up of retroactive interference compared to healthy individuals. It remains unclear whether abnormal memory interference is present at illness onset. This study investigated the nature and specificity of verbal memory interference in first-episode schizophrenia, and the specific cognitive and clinical correlates of interference. Build-up of PI, release from PI, and build-up of RI data in 72 geographically-represented FE schizophrenia patients recruited from a large catchment area were compared to that of 49 healthy controls and 43 FE bipolar patients matched on age, gender, premorbid IQ, and ethnicity. Results revealed similar verbal memory interference between groups. Although poorer cognitive flexibility and poorer verbal fluency reliably predicted less release from PI in FE patients, this finding was not unique to schizophrenia but rather characteristic of FE psychiatric illness in general. In contrast, poorer executive functioning was unrelated to build-up of RI. Clinical variables of interest (e.g., psychotic symptoms, antipsychotic medication) were largely unrelated to patients' susceptibility to interference. Importantly, susceptibility to memory interference did not predict eventual delayed verbal recall at illness onset, indicating that it is not a significant contributor to these patients' memory deficits. Given past findings of attenuated release from PI and heightened build-up of RI in chronic schizophrenia, these results suggest that abnormal memory interference in schizophrenia is not a core feature of the illness (e.g., an endophenotype) but rather develops over time with further illness burden and/or ongoing antipsychotic medications.

Keywords: Schizophrenia; first-episode; proactive interference; retroactive interference; executive functioning; symptoms

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List of Acronyms

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BPRS	Brief Psychiatric Rating Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
COWAT	Controlled Oral Word Association Test
CPZ	Chlorpromazine
CVLT	California Verbal Learning Test
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPII	Early Psychosis Identification and Intervention
FE	First episode
FEB	First-episode bipolar
FES	First-episode schizophrenia
FL	Frontal lobe
FP	Frontopolar
fMRI	Functional magnetic resonance imaging
HAM-D	Hamilton Rating Scale for Depression
HC	Healthy controls
IED	Intra-Extra Dimensional Set-Shifting
IQ	Intelligence quotient
IQR	Interquartile range
K-BIT	Kaufman Brief Intelligence Test
LDCR	Long-Delay Cued Recall
LDFR	Long-Delay Free Recall
LNS	Letter-Number Sequencing
LOC	Loss of consciousness
MINI	Mini-International Neuropsychiatric Interview
MRI	Magnetic resonance imaging
NAA	N-acetylaspartate
NAART	North American Adult Reading Test
OCD	Obsessive-compulsive disorder

OFC	Orbitofrontal cortex
PA	Paired-associates
PANSS	Positive and Negative Syndrome Scale
PI	Proactive interference
RAVLT	Rey Auditory Verbal Learning Test
RI	Retroactive interference
SCID	Structured Clinical Interview for DSM-III-R
SDCR	Short-Delay Cued Recall
SDFR	Short-Delay Free Recall
SPECT	Single photon emission computed tomography
STOP-EM	Systematic Treatment Optimization Program in Early Mania
TL	Temporal lobe
VLPFC	Ventrolateral prefrontal cortex
WAIS-III	Wechsler Adult Intelligence Scale-III
YMRS	Young Mania Rating Scale

Chapter 1.

Introduction

Since Emile Kraepelin began studying "Dementia Praecox" in the late 19th century, researchers have been interested in the cognitive deficits seen in what is now known as schizophrenia (Heinrichs & Zakzanis, 1998). Past research has shown that patients with this disorder exhibit impairment in a number of cognitive domains, such as general intelligence (Goldberg, Gold, Greenberg, & Griffin, 1993), memory (Aleman, Hijman, de Haan, & Kahn, 1999), attention (Braff, 1993), executive function (Morice & Delahunty, 1996), and language (Berlim, Mattevi, Belmonte-de-Abreu, & Crow, 2003). Such deficits are consistently reported in the literature and are moderate to large in magnitude (Heinrichs & Zakzanis, 1998).

Verbal memory deficits in particular are among the most powerful and robust findings of impairment in schizophrenia (Heinrichs, 2004). A meta-analysis by Aleman and colleagues (1999) was conducted on 70 studies that investigated the specific profile of memory impairment in this disorder. Their findings revealed moderately impaired verbal learning over repeated trials (d = -0.60), as well as severe deficits in both free recall (d = -1.27) and semantically cued recall (d = -0.95) following an immediate delay (i.e., short-term memory), and in both free recall (d = -1.20) and semantically cued recall (d = -0.78) following a long delay (i.e., long-term memory). Patients with schizophrenia also appear to demonstrate relatively less severe deficits in delayed recognition of verbal information, as evidenced by a more moderate effect size (d = -0.64). Importantly, moderate to large deficits are present at the first episode (FE; see Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009 for meta-analytic data), and prior to the commencement of antipsychotic treatment (Censits, Ragland, Gur, & Gur, 1997; Hill, Beers, Kmiec, Keshavan, & Sweeney, 2004; Saykin et al., 1994).

Moreover, research has shown that the degree of verbal memory impairment in patients with schizophrenia predicts their social and vocational functioning, social problem-solving, and skill acquisition (Bowie et al., 2008; Green, 1998; McClure et al., 2007; Milev, Ho, Arndt, & Andreasen, 2005), and is associated with more relapses during the early course of illness (Rund et al., 2007). Given its pervasiveness in this population and its impact on functional outcome, it is not surprising that researchers have attempted to determine the specific nature of verbal memory impairment in this disorder. The present study aimed to further elucidate the nature and specificity of verbal memory deficits in schizophrenia by investigating the extent to which interference effects underlie impaired recall of verbal information early in the course of illness.

Relevant Neuropathology in Schizophrenia

As illustrated in Table 1.1, schizophrenia is associated with abnormalities in the prefrontal-medial temporal-subcortical networks, which are known to underlie verbal memory processing. In healthy individuals, the prefrontal and medial temporal regions have been implicated in encoding of new episodic information, while the prefrontal, medial temporal, thalamic, and cerebellar regions have been implicated in episodic memory retrieval (see Fletcher, Frith, Rugg, 1997; Lepage, Habib, & Tulving, 1998; Nyberg & Cabeza, 2000; Spaniol et al., 2009; Straube, 2012; and Wagner, Koutstaal, & Schacter, 1999 for reviews). It is therefore not surprising that reduced prefrontal and hippocampal volumes, as well as greater basal ganglia volume (which is well connected to the prefrontal cortex), have been particularly associated with impaired verbal memory recall in schizophrenia (see Antonova, Sharma, Morris, & Kumari, 2004 for a review; Zipparo et al., 2008). Abnormalities in the above structures are found early in the course of illness (see Table 1.1), and single-sample studies that have directly compared chronic and FE patients have found minimal differences in hippocampal volumes between the two groups (right: d = -0.15, left: d = +0.13, Velakoulis et al., 1999; right: d = -0.05, left: d = +0.10, Wood et al., 2001). Putamen volumes, however, were found to be relatively larger in a single-sample of chronic patients with schizophrenia relative to those in their FE (d = +1.46), and are reportedly related to more prolonged antipsychotic use (Premkumar, Kumari, Corr, & Sharma, 2006). Relatively greater atrophy of the total prefrontal cortex (d = -0.74, Premkumar et al., 2006) and prefrontal gray matter (d =

Table 1.1. Relevant neuroanatomical abnormalities in schizophrenia.

	Primarily Chronic Samples[a]		FE Samples		
Structure/Function	**Cohen's *d***	***n***	**Cohen's *d***	***n***	**Study Authors**
Whole Brain	-0.30	3547	-0.26	686	De Peri et al. (2012)[b]
Left Lateral Ventricle	+0.51	557	+0.49	396	De Peri et al. (2012)[b]
Right Lateral Ventricle	+0.39	557	+0.40	396	De Peri et al. (2012)[b]
Third Ventricle	+0.60	820	+0.59	204	Vita et al. (2006)[b]
Prefrontal Cortex					
Gray Matter	-0.44	659			
White Matter	-0.29	511			
Total	-0.70	49	-0.42	34	Premkumar et al. (2006)
Left Hippocampus	-0.55	974	-0.66	187	Vita et al. (2006)[b]
Right Hippocampus	-0.58	922	-0.47	187	Vita et al. (2006)[b]
Left Amygdala	-0.39	481	-0.20	115	Vita et al. (2006)[b]
Right Amygdala	-0.38	548	-0.09	115	Vita et al. (2006)[b]
Thalamus[c]					
Left	-0.35	111	-0.34	25	Preuss et al. (2005)
Right	-0.31	111	-0.20	25	Preuss et al. (2005)
Total	-0.31	1168	-0.34	20	Cahn et al. (2002)
			-0.49	34	Premkumar et al. (2006)
			-0.41	21	Gur, Maany, et al. (1998)
Basal Ganglia[c]					
Left Caudate	+0.06	308	-0.21	30	DeLisi et al. (1991)
			-0.67	16	Keshavan et al. (1998)
			-0.64	12	Jayakumar et al. (2006)
Right Caudate	-0.06	308	-0.24	30	DeLisi et al. (1991)
			-0.83	16	Keshavan et al. (1998)
			-0.74	12	Jayakumar et al. (2006)
Total Caudate	-0.03	1101	+0.02	107	Lieberman et al. (2001)
			-0.49	18	Shihabuddin et al. (1998)
			-0.46	36	Corson et al.(1999)
			+0.03	20	Cahn et al. (2002)
Left Putamen	+0.21	169	-0.05	16	Keshavan et al. (1998)
Right Putamen	+0.24	169	-0.44	16	Keshavan et al. (1998)

Total Putamen	+0.10	950	+0.32	75	Gur, Maany, et al. (1998)
			+0.15	18	Shihabuddin et al. (1998)
Left Globus Pallidus	+1.06	36			
Right Globus Pallidus	+1.34	36			
Total Globus Pallidus	+0.26	510	+0.51	75	Gur, Maany, et al. (1998)

Note: Positive effect sizes denote volume increases whereas negative effect sizes denote volume decreases. FE = first episode.

[a] With the exception of the prefrontal cortex data (Premkumar et al., 2006), effect sizes are based on meta-analyses by Haijma et al. (2013), Davidson and Heinrichs (2003), and Wright et al. (2000),which includes mostly studies using chronic samples, but also some of FE samples.

[b] A meta-analysis of previous work. All other FE studies are based on single samples of patients.

[c] Usage of neuroleptic medication is associated with increases in structural volume, which may produce variability in measurements (Gur, Maany, et al., 1998; Haijma et al., 2013; Lang et al., 2004; Shenton, Dickey, Frumin, & McCarley, 2001; Wright et al., 2000).

-1.23, Premkumar et al., 2006) was also shown in the same sample of chronic patients relative to those in their FE, even after controlling for age and whole brain volume. Moreover, longitudinal studies over the first one to three years of illness have generally found specific decreases in prefrontal gray matter volume as illness duration progresses (Gur, Cowell, et al., 1998; Nakamura et al., 2007), although there is also evidence of decreases in temporal (Nakamura et al., 2007; Whitford et al., 2006) and parietal lobe volumes (Whitford et al., 2006). Nevertheless, deterioration of the frontal lobes appears to occur at a faster rate in the initial years of illness (Gur, Cowell, et al., 1998; Vita, De Peri, Deste, & Sacchetti, 2012), and seems to be related to cumulative dosage of antipsychotics even in the early course of illness (Cahn et al., 2002) [1].

In addition to the structural abnormalities seen in schizophrenia, there is meta-analytic evidence of lower N-acetylaspartate (NAA) in the prefrontal gray matter (*d* = -0.28; Steen, Hamer, & Lieberman, 2005), and abnormal frontal (especially prefrontal) brain metabolism and blood flow at rest (*d* = -0.65, Davidson & Heinrichs, 2003) and during cognitive tasks (*d* = -0.81, Davidson & Heinrichs, 2003), including encoding and retrieval of episodic information (Ragland et al., 2009; meta-analytic effect sizes were

[1] Based on a longitudinal study involving correlational analyses between magnetic resonance imaging (MRI) measured decreases in overall cortical gray matter volume from baseline to 1-year follow-up in FE schizophrenia patients and cumulative dosage of haloperidol equivalents during the same time period.

not provided). There is additionally evidence of reduced functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and both the bilateral thalamus and striatum using resting-state functional magnetic resonance imaging based on a single sample study (*d* = -1.22; Zhou et al., 2007). It is also worth noting that these functional deficits are present by the FE (Fusar-Poli et al., 2007; Steen et al., 2005; Zhou et al., 2007).

Memory Interference

Several potential mechanisms have been proposed to underlie verbal memory impairment in schizophrenia, some of which include difficulty selectively attending to stimuli (Brebion et al., 2000), slowed information processing (Andersen et al., 2013; Brebion, David, Bressan, & Pilowsky, 2007; Holthausen et al., 2003), impaired working memory (Stone, Gabrieli, Stebbins, & Sullivan, 1998), deficient processing of semantic information (Brebion, David, Jones, & Pilowsky, 2004; Hill et al., 2004), and deficits in some aspects of executive functioning, such as coordination and organization of information (Gsottschneider et al., 2011; Holthausen et al., 2003). Another perhaps more basic mechanism that may directly contribute to verbal memory impairment in schizophrenia is disproportionate interference of competing information on the acquisition and/or subsequent recall of target material.

In general, the concept of interference refers to goal-oriented performance decrements resulting from the hindrance of irrelevant, competing information or behaviour (Dempster & Corkill, 1999). An individual's ability to overcome interference is therefore crucial when performing goal-oriented behaviours, particularly given the plethora of information that we are inundated with in our daily lives. In fact, previous research has shown that interference from irrelevant distractors impacts performance on relatively higher cognitive functions, including working memory capacity (Jonides & Nee, 2006; Stone et al., 1998), selective attention (Aron, Sahakian, & Robbins, 2003), and speed of information processing (Lustig, Hasher, & Tonev, 2006), which have been associated with memory recall (as described in the preceding paragraph). Moreover, increased susceptibility to interference has been linked to abnormal prefrontal

functioning (Henson, Shallice, Josephs, & Dolan, 2002; Oztekin & Badre, 2011; Uhl, Podreka, & Deecke, 1994) and dopamine neurotransmission[2] (Fera et al., 2007; Montoya et al., 2008; Vernaleken et al., 2007). Given previous findings of dopamine deficiency in the prefrontal cortex in individuals with schizophrenia (Leuner & Muller, 2007; Toda & Abi-Dargham, 2007), one would expect that these patients might be particularly vulnerable to interference, which would consequently hinder verbal memory recall.

Interference is considered to be a normal process observed in healthy individuals of all ages (Geffen, Moar, O'Hanlon, Clark, & Geffen, 1990; Kramer & Delis, 1991; Wickens, 1970). There are two specific types of interference effects that have been posited to impede verbal memory. Specifically, proactive interference (PI) occurs when previously learned information hinders the recall of subsequent target information (Postman & Underwood, 1973; Wickens, 1970). In contrast, retroactive interference (RI) occurs when subsequent learning hinders the recall of previously learned target information (Postman & Underwood, 1973).

It is important to understand the mechanisms, or the process by which PI and RI occurs, as they appear to differ and may therefore be differentially impacted by the quality of deficits characterizing a disorder. More specifically, on list-learning and Wickens (1970) type paradigms[3], "build-up of PI" is observed when word recall decreases linearly over multiple successive trials of words belonging to the same semantic category (i.e., shared items). The mechanism underlying this "build-up" is due to increasing distraction from earlier trials, with recall of later trials suffering increasingly more than its preceding trials. Build-up of PI affects working memory capacity in healthy

[2] While reducing dopaminergic neurotransmission leads to greater susceptibility to interference (Fera et al., 2007; Montoya et al., 2008) and dopamine agonists reduce interference susceptibility (Barch & Carter, 2005; Vernaleken et al., 2007), there is evidence that overstimulation of dopamine receptors can also impair prefrontal functioning (Arnsten, 1997). Thus, there appears to be a dopamine range that is optimal for proper prefrontal functioning.

[3] Wickens-type tasks involve the consecutive presentation of multiple lists of semantically related items (i.e., shared items), one trial per list, followed by recall of the items after each trial. Participants are then presented with a final trial of items from a new semantic category (i.e., unshared items). In addition to assessing PI, list-learning tasks have the advantage of being amenable to assessing RI by having participants recall the original target information post-interference.

individuals by impeding one's ability to maintain focus of online target information, thus impacting recall (Jonides & Nee, 2006; Stone et al., 1998). Failure to develop PI is presumed to be due to impaired semantic encoding (Kareken, Moberg, & Gur, 1996; Wickens, 1970). Word recall dramatically improves, however, when a new semantic category is subsequently introduced. This "release from PI" occurs because the new target information is semantically distinct from the previous information (i.e., unshared items), thus making it less distracting. Successful release from PI requires one to adequately register the distinct semantic properties of the new items (thus making it available to aid retrieval; Freedman & Cermak, 1986), and to respond by flexibly shifting to recalling items from a new (and therefore less distracting) semantic category. This is supported by findings of an association between greater release from PI and better set-shifting abilities in clinical samples (Binetti et al., 1995; Moscovitch, 1982; Randolph, Gold, Carpenter, Goldberg, & Weinberger, 1992). Furthermore, it is important to recognize that the mechanisms underlying build-up of PI and release from PI (as described above) are not entirely overlapping, and abnormalities in these two constructs do not necessarily co-occur. For example, there have been findings of normal build-up of PI but reduced release in some clinical populations, such as in persons with multiple sclerosis (e.g., Griffiths et al., 2005) whereas other samples, such as those with chronic alcoholism, have exhibited abnormal build-up of PI but normal release (e.g., Blusewicz, Kramer, & Delmonico,1996).

In contrast, "build-up of RI" is observed when new learning hinders the recall of previously learned target information. The mechanisms underlying this type of interference appear to involve a number of executive functions, including one's ability to monitor the source of presented information, to remember the temporal order of items presented, to mentally shift back to recalling the original target items following interference, and to fluently verbalize target items post-interference[4] (Marsh, Landau, & Hicks, 1996; Torres, Flashman, O'Leary, & Andreasen, 2001). Impairment in these executive abilities would be expected to further impede the post-interference recall of

[4] Although RI effects have been correlated with phonemic fluency, this association may not seem as intuitive as its relation to other executive functions. However, phonemic fluency relies on effortful self-initiation while monitoring and inhibiting inappropriate responding (Henry & Crawford, 2004). Thus, poor verbal fluency abilities might further impede one's ability to self-initiate recall of target items while inhibiting similar, distracting material.

target information, thus increasing vulnerability to RI. Although there are no known studies that have examined the association between executive functioning and all three interference effects (i.e., build-up of PI, release from PI, and build-up of RI), past research has demonstrated that overall word recall on the RI trial (but not the PI trial) decreases with poorer executive functions (Torres et al., 2001), which suggests that RI is relatively more dependent on intact executive functioning than PI. Although release from PI is indeed associated with intact set-shifting abilities, it may be the case that set-shifting abilities are relatively more critical to build-up of RI since individuals must shift back to recalling information prior to the interference list, rather than shifting forward to a new list as is the case for release from PI.

Neuroimaging research in healthy individuals and lesion studies with clinical samples have typically implicated the involvement of the prefronto-thalamic network in the aforementioned interference effects on verbal memory (see Table 1.2). Specifically, these findings suggest that the presence of interfering information activates the prefronto-thalamic network during verbal memory tasks, and that abnormalities in this network heightens one's susceptibility to memory interference. Moreover, studies employing clinical populations that typically exhibit frontal disease have shown further evidence of disproportionate interference effects on memory, including increased build-up of PI and RI in chronic alcoholism (Blusewicz et al., 1996), reduced release from PI in Korsakoff's Disease (Freedman & Cermak, 1986; Squire, 1982), reduced release from PI and greater build-up of RI in multiple sclerosis (Griffiths et al., 2005), and increased build-up of RI in traumatic brain injury (Vanderploeg, Crowell, & Curtiss, 2001).

Importantly, individuals with schizophrenia would likely be particularly susceptible to memory interference. Firstly, these individuals typically have prefrontal, thalamic, and dopaminergic abnormalities that would presumably make them disproportionately susceptible to the detrimental impact of interference on memory (as described above). Secondly, individuals with schizophrenia have abnormal activation of semantic networks, as well as difficulty processing and using semantic information (see Mohammad & DeLisi, 2013 for a review), which may make it more difficult for them to adequately register the distinct semantic properties of the new, less distracting, items on the release from PI trial in order to facilitate retrieval. Thirdly, schizophrenia patients typically have notable deficits in tasks thought to entail prefrontal functioning (e.g., working memory,

Table 1.2. Implicated brain structures related to memory interference.

Study	Sample of Interest	Nature of Study	Results[a]	Implicated Structure
Uhl et al. (1994)	Healthy adults	SPECT, PA	↑ blood flow in R anterior middle FL & trend L thalamus during PI	Anterior middle FL & thalamus
Henson et al. (2002)	Healthy adults	Event-related fMRI, PA	↓ activation in L inferior FL (low interference) and ↑ bilateral FP & ↑ R DLPFC during PI (high interference)	Inferior FL, FP, & DLPFC
Oztekin & Badre (2011)	Healthy adults	fMRI, list-learning	L VLPFC activation mediated relation between ↑ PI and ↓ in memory performance	VLPFC
Moscovitch (1982)	Unilateral FL vs. TL lobectomy	List-learning	↓ release from PI	FL
Stuss et al. (1982)	Schizophrenia patients with bilateral OFC leucotomy	Consonant trigrams	↑ build-up of PI	OFC
Freedman & Cermak (1986)	Bilateral FL lesions & poor memory	Wickens	↓ release from PI	FL
Janowsky et al. (1989)	FL lesions	Word trigrams	Normal release from PI	Not Applicable
Gershberg & Shimamura (1995)	Unilateral DLPFC lesions	List-learning	↑ build-up of PI	DLPFC
Shimamura et al. (1995)	DLPFC lesions	PA	↑ build-up of PI	DLPFC
McDonald et al. (2001)	Unilateral prefrontal vs. TL resection	CVLT	↓ release from PI	Prefrontal cortex
Baldo et al. (2002)	Unilateral FL lesions	CVLT-II	Normal PI[b]	Not Applicable

Note: SPECT = single photon emission computed tomography; PA = paired-associates; R = right; L = left; fMRI = functional magnetic resonance imaging; DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; OFC = orbitofrontal cortex; FL = frontal lobe; FP = frontopolar; TL = temporal lobe; CVLT = California Verbal Learning Test; PI = proactive interference.

[a] All interference effects examined in each study are reported.

[b] Did not examine shared and unshared items separately.

set-shifting, and verbal fluency; Heinrichs & Zakzanis, 1998; Ma et al., 2007; Mesholam-Gately et al., 2009; Reichenberg & Harvey, 2007; Riley et al., 2000), and these deficits are known to negatively impact memory interference (as described above). And fourthly,

schizophrenia by definition is associated with a constellation of psychotic symptoms, including auditory hallucinations and disorganized thought processing, that would likely be particularly taxing on the already limited cognitive resources available to these patients when learning and remembering target information in the face of distraction.

It is therefore not surprising that the majority of previous studies using list-learning or Wickens tasks found medium to large effects sizes for increased build-up of RI and decreased release from PI in multiple episode schizophrenia relative to healthy controls, while studies with large sample sizes have found normal build-up of PI or, at best, a small effect for decreased build-up of PI in schizophrenia patients relative to healthy controls (see Table 1.3 for a comprehensive list). Moreover, reduced release from PI has been demonstrated in schizophrenia patients with known set-shifting deficits (e.g., Randolph et al., 1992), and increased build-up of RI has been shown to be related to reduced set-shifting abilities, phonemic fluency, and accuracy of temporal order judgments in this disorder (Torres et al., 2001). Similarly, the limited research investigating the relation between psychotic symptoms and memory interference has suggested associations between less release from PI and a greater number of negative symptoms (which consist of deficits such as blunted affect, motor retardation, and lack of spontaneity; Guillem et al., 2001) and the presence of thought disorder (which is a symptom of disorganization; Kay, 1982) in chronic schizophrenia patients. On the other hand, greater build-up of PI has been associated with more severe auditory hallucinations (which is a positive symptom of psychosis that comprises an excess; Guillem, Rinaldi, Pampoulova, & Stip, 2008) and symptoms of disorganization (Guillem et al., 2001; Guillem et al., 2008). In contrast, the few studies that have examined the relation between build-up of RI and psychotic symptoms have found no association (Hill et al., 2004; Moritz, Heeren, Andresen, & Krausz, 2001).

Table 1.3. Memory interference effects in multiple episode schizophrenia.

Study	Patient *n*	Nature of Task	Cohen's *d*
Build-Up of PI			
Torres et al. (2001)	143	RAVLT	-0.26
Paulsen et al. (1995)	175	CVLT	-0.23
Alfimova et al. (2010)	405	Word list-learning task	+0.20*
Moritz et al. (2001)	25	RAVLT	+0.34
O'Carroll et al. (1993)	10	RAVLT	+0.49
Kareken et al. (1996)[a]	29	CVLT	+0.80*
Release from PI			
Randolph et al. (1992)	16	Wickens	-0.80*
Kay (1982)[b]	42	Wickens	-0.72*
Kareken et al. (1996)[a]	29	CVLT	-0.23
Build-Up of RI			
Sengel et al. (1985)	23	Word list-learning task	-1.00*
Kareken et al. (1996)[a]	29	CVLT	-0.69*
Moritz et al. (2001)	25	RAVLT	-0.58
Torres et al. (2001)	143	RAVLT	-0.46*

Note: CVLT = California Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test; PI = proactive interference; RI = retroactive interference.

* Studies in which the authors found statistically significant effects.

[a] Examined shared and unshared items separately.

[b] Compared to a non-schizophrenia psychotic control group

First Episode Schizophrenia

Nonetheless, the majority of past studies examining PI and/or RI in schizophrenia have employed chronic samples of patients who have been treated with antipsychotic medication for many years. This raises the possibility that heightened susceptibility to memory interference may develop over time due to illness progression, repeated psychotic episodes, and/or ongoing medication treatment, which may lead to further deterioration of the prefrontal lobes and thus greater vulnerability to interference from competing information. On the other hand, interference effects on memory might instead be an early core deficit that is present at illness onset, before chronic illness burden and long-term antipsychotic treatment. This is important as such findings of early deficits give insight into potential avenues for early intervention (Gopal & Variend, 2005;

Lewis, Tarrier, & Drake, 2005). One way to circumvent the confounding effects of chronic illness burden, repeated hospitalizations, and long-term antipsychotic treatment is to study patients during their FE of psychosis.

As previously mentioned, there is evidence of considerable verbal memory impairment and prefrontal abnormalities in FE schizophrenia. Nonetheless, there is little research examining verbal memory interference at illness onset. Hill and colleagues (2004) administered the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) to 62 antipsychotic-naive FE schizophrenia patients and 67 healthy controls to characterize the nature of verbal memory deficits in this population. They evaluated build-up of PI and RI using simple difference scores, a relatively common but less sensitive measure of interference effects than Kramer and Delis (1991)'s method of separately evaluating shared and unshared list items[5]. No significant differences between FE patients and healthy controls were observed (PI: d = -0.24; RI: d = -0.31).

In contrast, Sitskoorn, Nuyen, Appels, van der Wee, and Kahn (2002) compared build-up and release from PI in 35 FE schizophrenia patients, 20 individuals with obsessive-compulsive disorder (OCD), and 34 healthy controls using the Dutch version of the CVLT. Unlike Hill et al.'s (2004) study, these authors analyzed the items from shared and unshared categories separately to determine build-up of and release from PI. As seen in chronic samples, FE patients with schizophrenia demonstrated normal build-up of PI, but reduced release from PI relative to healthy controls (d = -0.71) and individuals with OCD (d = -0.54), who performed similarly to each other. Build-up of RI was not examined. It is worth noting that Sitskoorn et al.'s (2002) findings have not yet been replicated.

[5] The Kramer and Delis (1991) method separately evaluates interference resulting from shared (i.e., semantically related) and unshared (i.e., semantically unrelated) items between lists to deconstruct PI into build-up of PI and release from PI, and RI into shared versus unshared items. Although significant findings using traditional difference scores would indeed be indicative of build-up in PI or RI, they may be less sensitive since interference is greatest when competing information is semantically similar (Wickens, 1970), which may not always be detected when shared and unshared items are combined. This has been confirmed in both healthy individuals and those with traumatic brain injury by demonstrating PI using the Kramer and Delis (1991) method while not observing PI in the same samples using the traditional difference method (Numan, Sweet, & Ranganath, 2000).

Research Gaps

Taken together, there is only limited research on the effects of PI and RI on verbal memory in FE schizophrenia. The following gaps exist in this literature:

1. No study has comprehensively examined interference effects (build-up of RI and PI, and release from PI) within the same sample of patients, and there is no research on whether RI effects are disproportionately greater for shared versus unshared items. It is important to investigate the presence/absence of all interference effects, as they appear to involve relatively different mechanisms that may be differentially impacted by the disorder.
2. The specificity of verbal memory interference in FE schizophrenia is unclear. Addressing this issue would help to elucidate the extent to which abnormal susceptibility to interference is unique to FE schizophrenia or is instead characteristic of early psychiatric illness in general. Although Sitskoorn et al.'s (2002) study included a sample of OCD patients, they did not specify their illness duration, and thus it is unclear how far into their illness they had progressed. Nevertheless, FE bipolar patients may provide an even better comparison to FE schizophrenia patients, given the many neuropathological, cognitive, clinical, and genetic similarities inherently found between the two disorders. For example, bipolar disorder has also been associated with reduced prefrontal volumes, reduced NAA, and abnormal prefrontal metabolism and blood flow at rest and during cognitive tasks (for reviews, see Soares & Mann, 1997 and Strakowski, DelBello, & Adler, 2005), and evidence of prefrontal pathology has been found at the FE (e.g., Adler et al., 2006; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Yatham et al., 2007). Deficits in verbal memory, working memory, set-shifting, and verbal fluency are also present at the FE (Gruber, Rosso, & Yurgelun-Todd, 2008; McClellan, Prezbindowski, Breiger, & McCurry, 2004; Torres et al., 2010)[6]. Despite these similarities, schizophrenia patients have been shown to have relatively lower prefrontal volumes than bipolar patients, even at illness onset (e.g., Farrow et al., 2005). Moreover, schizophrenia patients typically have greater deficits in verbal memory, working memory, set-shifting, and verbal fluency than do bipolar patients (for meta-analytic data, see Krabbendam, Arts, van

[6] Other similarities include reduced whole brain volume (De Peri et al., 2012), and increased thalamic (Adler et al., 2007) and striatal volumes (Kozicky et al., 2013) present at the FE, as well as similar lifetime prevalence rates, age of illness onset, and overlapping symptoms (e.g., psychosis and depression; American Psychiatric Association, 1994). There is also evidence of genetic overlap (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002), which is thought to underlie the development of psychosis in general, with other genes and/or environmental factors launching an individual on a trajectory of either schizophrenia or bipolar disorder (Murray et al., 2004; Walker, Curtis, & Murray, 2002).

Os, Aleman, 2005). Although fewer studies have directly compared these cognitive abilities in FE samples, there is evidence that suggests they are relatively worse in schizophrenia (Barrett, Mulholland, Cooper, & Rushe, 2009; Hill et al., 2009; Mojtabai et al., 2000; Zanelli et al., 2010)[7]. Taken together, these findings suggest that, while FE bipolar patients would likely also be abnormally vulnerable to memory interference, they may be relatively less vulnerable than FE schizophrenia patients due to their relatively less severe structural and functional abnormalities of the prefrontal cortex. While there has been very little research investigating memory interference in chronic bipolar disorder and no known studies employing FE bipolar patients, there does appear to be some evidence to suggest that bipolar patients have increased build-up of RI that may be marginally lower than nonparanoid schizophrenia patients (Sengel, Lovallo, & Pishkin, 1985).

3. It is unclear whether deficits in tasks thought to entail prefrontal functioning (e.g., working memory, executive functioning) predict memory interference during the FE of schizophrenia, despite findings implicating a detrimental impact of executive functioning deficits on release from PI and build-up of RI in chronic patients with the illness (Randolph et al., 1992; Torres et al., 2001).
4. It remains unclear whether memory interference varies as a function of symptom type and severity in FE schizophrenia, despite findings of associations between various symptom dimensions and PI in chronic samples (Guillem et al., 2001; Guillem et al., 2008; Kay, 1982). This would have important implications on the pervasiveness of abnormal interference susceptibility and its potential to improve with the resolution of certain types of clinical symptoms in the early course of illness.
5. The extent to which PI and RI predict long-term delayed recall of verbal information early in the course of illness remains unclear. This is important as it would help to clarify the extent to which abnormal susceptibility to interference underlies impaired verbal memory recall at illness onset.

[7] Other differences include greater ventricular enlargements (Videbech, 1997), reduced whole cerebral volume (Norris, Krishnan, & Ahearn, 1997), and thalamic abnormalities (Norris et al., 1997; Strakowski et al., 2005) in schizophrenia relative to bipolar disorder, though these findings have not been consistently found when directly comparing FE samples (e.g., Nakamura et al., 2007; Rosa et al., 2010). Greater temporal lobe abnormalities have been found in FE schizophrenia patients relative to FE bipolar patients (Hirayasu et al., 1998; Qiu, Gan, Wang, & Sim, 2013). Unlike schizophrenia, bipolar disorder is associated with increased signal hyperintensities in the periventricular white matter, subcortical grey matter, and deep white matter of the bilateral frontal and fronto-parietal junction (Norris et al., 1997), which has been related to impaired frontal functioning (Videbech, 1997). Evidence of white matter pathology has been found even in the FE (Adler et al., 2006).

Objectives

In addition to verifying Sitskoorn et al. (2002)'s findings of relatively normal build-up of PI but diminished release from PI in FE schizophrenia, the current study aimed to extend previous research on verbal memory interference at illness onset by addressing numerous gaps in the literature. There were three main goals of this study: 1) to clarify the extent to which schizophrenia patients exhibit abnormal verbal memory interference at illness onset; 2) to clarify the specificity of interference effects in the early course of schizophrenia; and 3) to identify specific cognitive and clinical correlates of memory interference during the FE of schizophrenia.

Hypotheses

1. Based on past findings of an association between poorer executive functioning and both attenuated release from PI (Binetti et al., 1995; Moscovitch, 1982; Randolph et al., 1992) and greater build-up of RI (Marsh et al., 1996; Torres et al., 2001), it was predicted that FE schizophrenia patients (like their chronic counterparts) would exhibit heightened build-up of RI for shared versus unshared items, as well as attenuated release from PI (but normal build-up of PI), when compared to healthy controls. Such findings of increased susceptibility to memory interference effects at illness onset would further establish that interference is an early manifestation of the disorder that cannot solely be attributed to secondary effects of illness progression, repeated psychotic episodes, and ongoing antipsychotic treatment. Ultimately, such findings would help to elucidate the specific mechanisms that hinder learning and recall of verbal information in schizophrenia, thereby giving insight into potential avenues for early intervention.
2. There is very little research examining verbal memory interference in bipolar disorder, and therefore the extent to which these patients have abnormal interference remains unclear. Nevertheless, bipolar patients are known to exhibit notable verbal memory impairment, prefrontal abnormalities, and deficits on tasks that entail prefrontal functioning, which are generally similar to those with schizophrenia, albeit with quantitatively less impairment. It was therefore predicted that FE patients with bipolar disorder would exhibit a similar pattern of interference effects that are intermediate to that of FE patients with schizophrenia and healthy controls, given that prefrontal functioning appears to be relatively more impaired in schizophrenia than in bipolar disorder and that intact prefrontal functioning is needed for adequate recall despite interference. Such a pattern of differential performance

between these three groups would lend further support to the contention that prefrontal functioning is an important determinant of verbal memory interference.

3. Consistent with previous research in chronic schizophrenia and other clinical samples, it was hypothesized that lower release from PI would be associated with greater deficits in cognitive flexibility/set-shifting, whereas increased build-up of RI would be associated with deficits in both cognitive flexibility/set-shifting and verbal fluency in FE schizophrenia. In other words, deficits in set-shifting ability were expected to hinder one's ability to both flexibly shift to recalling target items from different semantic categories on the PI trial in order to aid retrieval (as they are less distracting than semantically related information) and also to shift back to recalling original target information on the RI trial after being presented with interfering material. Verbal fluency deficits were expected to hinder their ability to self-initiate recall of previously learned target items while inhibiting the recall of recently presented distracting material during the RI trial. Consistent with past research showing no association between phonemic fluency and release from PI (Binetti et al., 1995; Parkin & Lawrence, 1994; Randolph et al., 1992), it was expected that patients would be sufficiently able to inhibit inappropriate responses when self-initiating recall of new target stimuli than when self-initiating recall of previously learned targets following distraction as is the case for the RI trial. Moreover, the overall pattern of associations between executive functioning and verbal memory interference would lend further support to the contention that prefrontal functioning is a critical determinant of memory interference, as the latter executive functions are thought to be sensitive to prefrontal functioning.

Secondary Investigations

1. This study explored whether various clinical variables of interest were associated with memory interference effects in FE schizophrenia. For example, while it was anticipated that build-up of RI would not be associated with psychotic symptoms, it was expected that greater build-up of PI would be associated with more severe positive symptoms and disorganization and that less release from PI would be associated with more severe negative symptoms and disorganization. Moreover, it was expected that greater exposure to antipsychotics (e.g., chlorpromazine equivalents, duration of time on antipsychotics) would be related to greater verbal memory interference.
2. This study also explored whether interference is a significant contributor to delayed verbal memory in FE schizophrenia, and would thus predict long delay free recall performance on the CVLT-II. Considering both the interference and the delayed memory scores are derived from the same cognitive measure, this study explored this

association using relative interference difference scores instead of raw interference scores, as raw scores are inherently reliant on baseline recall ability (see methods section).

Chapter 2.

Methodology

Participants

The number of participants required to achieve a power of approximately .80 was calculated using Cohen's (1988) power tables for F tests on means in the Analysis of Variance and Covariance, with an alpha = .05 and a u = 2 (i.e., degrees of freedom for the numerator of the F ratio). A medium to large effect size was estimated (*f* = 0.30) based on the aforementioned evidence of medium to large effects for RI and release from PI in chronic schizophrenia (see Table 1.3) and preliminary evidence of a medium to large effect for release from PI in FE schizophrenia (*d* = -0.71; Sitskoorn et al., 2002). Results of the a priori power analysis suggested required sample sizes of at least 36 participants per group.

Data from 72 FE patients meeting *DSM-IV* criteria of schizophrenia or schizoaffective disorder and 65 FE patients meeting *DSM-IV* criteria of bipolar disorder were drawn from two previously ascertained databases of FE patients. The first original database included data of geographically-represented FE psychosis patients recruited into the Early Psychosis Identification and Intervention (EPII) program between 2001 and 2006. The EPII program serves a catchment area population of approximately 640,000 in the Greater Vancouver area. Approximately 81 FE patients per year enter the program, most of whom have diagnoses of schizophrenia or schizoaffective disorder. Diagnostic information was obtained through patient and family interviews conducted by a research psychiatrist and a Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, & First, 1992) completed by a psychologist. Patients were seen at least monthly for clinical follow-up. Final DSM-IV diagnoses were made at a consensus conference 9-12 months post-onset using all available clinical and research information obtained since illness onset.

The second original database included sample of convenience data of FE bipolar patients recruited from the Systematic Treatment Optimization Program in Early Mania (STOP-EM) at the University of British Columbia and the Vancouver General Hospitals and affiliated sites, as well as by community and hospital referrals from physicians and psychiatrists. Data was collected between 2004 and 2011. DSM-IV diagnostic information was obtained through a comprehensive interview conducted by a research psychiatrist and a Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Patients were required to be sufficiently clinically stable to undergo cognitive testing. The protocols from both original studies were approved by the research ethics boards at Simon Fraser University and the University of British Columbia.

The patients drawn from both original studies were required to have experienced their FE within the three months preceding enrolment into the study. Exclusion criteria for the current study included: 1) a diagnosis of substance-induced psychotic disorder (according to *DSM-IV* criteria), 2) a history of neurological or medical illness known to impact brain functioning (e.g., meningitis, encephalitis, diabetes), 3) reasonable evidence of previous head injury with loss of consciousness for more than 5 minutes, 4) a composite IQ below 65 as measured by the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990), 5) a previous diagnosis of a manic episode (that is, prior to the index episode), and 6) a previous diagnosis of a psychotic episode (that is, prior to the index episode). Figure 2.1 illustrates the attrition of patients from the two original studies with which the current data is drawn.

Similarly, data from 105 healthy controls were also drawn from the same two original databases as the FE patients. Healthy controls were recruited from the community through word of mouth and advertisements posted at the University of British Columbia and affiliated sites. They were required to meet the same exclusion criteria as the patient samples, with the additional exclusion of a personal history of psychiatric illness and a familial history of schizophrenia spectrum disorder or bipolar disorder in first degree relatives. All participants were fluent in English.

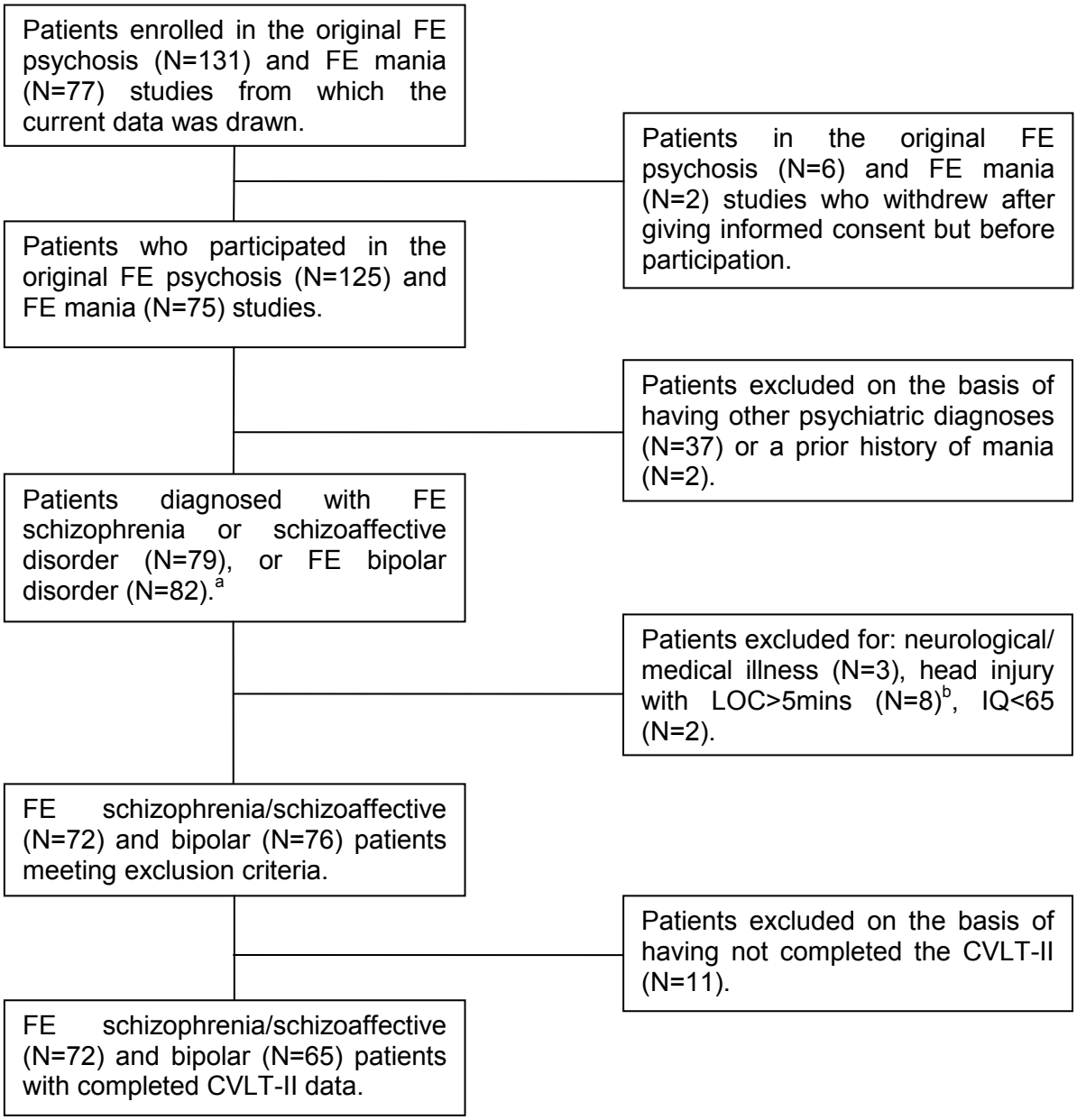

Figure 2.1. Flowchart of attrition in FE samples.

[a] Bipolar patients were drawn from both the original FE psychosis and FE mania studies.
[b] Length of loss of consciousness (LOC) either at least 15 minutes or unknown.

Symptom Ratings

Overall symptom severity was assessed in FE samples using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1988). This scale is comprised of 18 items designed to measure the presence/absence and severity of psychiatric symptoms. Each item is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extreme severity. Twenty-seven percent of FE patients were tested within four days of their symptom ratings, 34% within one week, 57% within two weeks, and 70% within three weeks. Of note, the number of days elapsed between BPRS ratings and cognitive testing was not significantly associated with BPRS scores, r = -0.10, p = .275, indicating that longer time lags between symptom ratings and testing did not significantly influence the patients' symptom ratings.

Psychiatric symptoms in the FE schizophrenia patients were also assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). This scale is comprised of 30 items designed to measure the presence/absence and severity of psychiatric symptoms common to schizophrenia. Each item is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extreme severity. Based on factor-analytic data presented by van der Gaag et al. (2006), symptom dimension scores were computed using the following PANSS items: 1) Delusions, Hallucinatory Behavior, Unusual Thought Content, Suspiciousness, Grandiosity, Somatic Concern, Lack of Judgment & Insight, Active Social Avoidance, and Difficulty in Abstract Thinking (subtracted) for positive symptoms; 2) Lack of Spontaneity & Flow of Conversation, Blunted Affect, Emotional Withdrawal, Passive-Apathetic Social Withdrawal, Motor Retardation, Poor Rapport, Active Social Avoidance, Uncooperativeness, Disturbance of Volition, and Conceptual Disorganization (subtracted) for negative symptoms; and 3) Stereotyped Thinking, Poor Attention, Disorientation, Conceptual Disorganization, Difficulty in Abstract Thinking, Mannerisms & Posturing, Lack of Judgment & Insight, Disturbance of Volition, Preoccupation, and Unusual Thought Content for symptoms of disorganization. Twenty-four percent of FE schizophrenia patients were tested within four days of their symptom ratings, 35% within one week, 64% within two weeks, and 82% within three weeks. Of note, the number of

days elapsed between PANSS ratings and cognitive testing was not significantly associated with PANSS total scores, $r = 0.10$, $p = .386$, positive symptoms, $r = 0.09$, $p = .464$, negative symptoms, $r = 0.12$, $p = .328$, or disorganization symptoms, $r = 0.05$, $p = .684$, indicating that longer time lags between symptom ratings and testing did not significantly influence the patients' symptom ratings.

Mood symptoms were also assessed in the FE bipolar patients enrolled in the original first episode mania study from which the current data were drawn. Specifically, severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). This scale is comprised of 11 items, rated on a 5-point scale, and is designed to measure the severity of current manic symptoms. Moreover, severity of depressive symptoms was assessed using the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). This scale is comprised of 21 items, rated on either a 3- to 5-point scale, and is designed to measure the severity of depressive symptoms. Fifty-five percent of patients were tested within four days of their mood ratings, 62% within one week, and 80% within two weeks. Of note, the number of days elapsed between symptom ratings and cognitive testing was not significantly associated with either YMRS scores, $r = 0.09$, $p = .529$, or HAM-D scores, $r = 0.05$, $p = .733$, indicating that longer time lags between symptom ratings and testing did not significantly influence the patients' symptom ratings.

Cognitive Measures

Verbal Memory Assessment

Verbal learning and memory were assessed using the California Verbal Learning Test, 2nd edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II is a list-learning test that consists of 16 words (List A), four words from each of four semantic categories (e.g., furniture, vegetables, ways of traveling, animals). Participants are presented with the same list five times (Trials 1-5), and are instructed to recall as many of the items as they can, in any order, after each presentation. Following Trial 5 of the learning trials, participants are immediately presented with a new “interference” list of 16 words (List B) with four words from each of four semantic categories. Two of the List B

categories are the same as two of the List A categories (e.g., vegetables, animals) and are thus referred to as “shared” categories, whereas the other two List B categories are different than the remaining List A categories (e.g., musical instruments, parts of a house) and are referred to as “unshared” categories. Immediately following the recall of List B, participants are asked to recall the items from List A in a free recall format (i.e., Short-Delay Free Recall), followed by a cued recall format (i.e., Short-Delay Cued Recall). After a 20 minute delay, participants are again asked to recall the items from List A using a free recall format (i.e., Long-Delay Free Recall), and a cued recall format (i.e., Long-Delay Cued Recall). Participants then complete a recognition test that includes all the words from List A and List B, as well as an additional 16 distractor words that are either semantically related to the words on List A or semantically unrelated to the words on List A and List B. Participants are asked to report whether or not each word was from the original list (List A).

There are two comparable forms of the CVLT-II: 1) the standard form and 2) the alternate form, which were designed to reduce practice effects on follow-up testing. These forms differ only in the actual words and the semantic categories presented on List A and List B. Previous research has demonstrated acceptable alternate form reliability of the CVLT-II, with particularly robust reliability coefficients for key CVLT-II variables (e.g., List A Trials 1-5, Short Delay Free Recall, Long Delay Free Recall, and Recognition Discriminability; ranging between .72 and .79); Delis et al., 2000). Moreover, all reliability coefficients for the trials that make up the interference effects are adequate, with coefficients ranging between .51 (List B) and .73 (Short Delay Free Recall). Of note, the original FE psychosis study from which the current data were drawn gave half of their participants the standard form of the CVLT-II and the other half received the alternative form, whereas all of the participants in the original FE mania study were given the CVLT-II standard form.

Working Memory/Executive Functioning Measures

The following three cognitive abilities thought to entail prefrontal functioning were examined: 1) working memory, 2) cognitive flexibility/set shifting, and 3) verbal fluency.

Working memory. Working memory was assessed using the Letter-Number Sequencing subtest from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III; Wechsler, 1997). This task requires participants to order sequentially a series of letters and numbers that are presented orally, and yields the total number of correctly completed sequences.

Cognitive flexibility/set-shifting. Cognitive flexibility and set-shifting were assessed using the Intra-Extra Dimensional Set Shifting (IED) subtest from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins et al., 1994). This test involves flexibly shifting between intra-dimensional and extra-dimensional sets, and yields the total number of errors adjusted, which adjusts for the number of levels successfully completed[8]. Of note, this task is a computerized analogue of the Wisconsin Card Sorting Task and has been shown to be sensitive to set-shifting deficits in schizophrenia patients (Levaux et al., 2007).

Verbal fluency. Phonemic fluency was assessed using the Controlled Oral Word Association Test (COWAT; Lezak, 1995), which measures the total number of words produced in one minute for each of the letters F, A, and S. Generated words cannot be proper names, exact repetitions, or the same word with a different ending (e.g., eat, eating, eaten).

Estimated Premorbid IQ

The North American Adult Reading Test (NAART; Blair & Spreen, 1989), which involves reading a list of 61 irregular words, was used to estimate premorbid intellectual functioning.

[8] The IED total number of errors adjusted score is calculated by adding 25 for each stage not attempted due to failure. This value is used because participants must complete 50 trials to fail a stage and half of these could be correct by chance alone.

Calculation of Interference Effects

In accordance with Kramer and Delis (1991), PI was assessed by comparing the number of shared/unshared items recalled on List A Trial 1 with the number of shared/unshared items recalled on List B of the CVLT-II. More specifically, reduced recall of shared items on List B relative to shared items recalled on List A Trial 1 indicates build-up of PI, whereas equivalent or greater recall of unshared items on List B relative to unshared items on List A reflects release from PI. Retroactive interference is present when the recall of items on List A Short-Delay Free Recall is lower than the recall of items on List A Trial 5, with greater declines in recall expected for shared relative to unshared items (Kramer & Delis, 1991). It has been argued that the relative proportion of shared and unshared items recalled across the five learning trials of List A affects the corresponding potential for build-up of PI and release from PI during List B recall and also for RI during the Short-Delay Free Recall trial of List A (Kramer & Delis, 1991). Thus, instead of using raw word counts in the main analysis of variance (ANOVA) model described below, this potential confound was controlled for by using the following weighted average of shared and unshared category items for List A Trial 1 (i.e., List A-1) for PI (based on Kramer & Delis, 1991):

$$\text{Weighted Average of Shared Items} = \text{List A-1 Recall} \times \left(\frac{\text{Shared Trials 1-5 Recall}}{\text{Total Trials 1-5 Recall}} \right)$$

$$\text{Weighted Average of Unshared Items} = \text{List A-1 Recall} \times \left(\frac{\text{Unshared Trials 1-5 Recall}}{\text{Total Trials 1-5 Recall}} \right)$$

Similarly, the weighted average of shared and unshared category items for List A Trial 5 (i.e., List A-5) for RI were calculated as follows (based on Kramer & Delis, 1991):

$$\text{Weighted Average of Shared Items} = \text{List A-5 Recall} \times \left(\frac{\text{Shared Trials 1-5 Recall}}{\text{Total Trials 1-5 Recall}} \right)$$

$$\text{Weighted Average of Unshared Items} = \text{List A-5 Recall} \times \left(\frac{\text{Unshared Trials 1-5 Recall}}{\text{Total Trials 1-5 Recall}} \right)$$

Relative Individual Difference Scores for Interference

In order to evaluate the degree to which interference effects are related to working memory/executive functioning, clinical variables of interest, and long-term verbal memory, relative individual interference difference scores (as opposed to absolute, or raw, difference scores) were computed for each participant to control for differences in baseline performance (i.e., List A Trial 1 for PI and List A Trial 5 for RI). This is important as differences in baseline performance may potentially confound interference scores that are based on raw trial-to-trial comparisons (Griffiths et al., 2005; Torres et al., 2001). For example, poor baseline recall truncates the extent to which interference-related declines in recall can occur, while higher baseline recall allows for greater differences in raw scores reflecting interference. Thus, the use of relative difference scores permits the calculation of interference-related changes in recall, while accounting for baseline performance[9]. Of note, these relative individual difference scores differ from the weighted averages of shared and unshared category items (described in the preceding section) as the latter scores do not control for differences in overall baseline memory performance but rather controls for the relative proportion of shared versus unshared items one recalls across the five learning trials of List A and corresponding differences in the potential for build-up and release from interference.

Items on the CVLT-II are of similar recall difficulty (Delis et al., 2000) and as such the most stable estimate of how many shared or unshared items each individual "should" be capable of recalling on any particular trial is the average of shared and unshared

[9] The rationale for using relative difference scores instead of raw, absolute scores can be best understood when considering the difference scores between 100-99 and 2-1. While the absolute difference in both cases equals 1, their relative difference is far from equal (i.e., [100-99] / 100 = 0.01 and [2-1] / 2 = 0.50, respectively).

items recalled on the baseline trial. In accordance with Griffiths and colleagues (2005), this estimate can be compared with the individual's actual raw recall of shared or unshared items on List B for PI estimates and on Short-Delay Free Recall of List A for RI (i.e., raw trial recall score, not weighted averages described earlier). Thus, relative individual interference difference scores for PI and RI were calculated as follows:

$$\text{Build-up of PI} = \frac{\left[\frac{\text{Shared List A-1 Recall} + \text{Unshared List A-1 Recall}}{2}\right] - \text{List B Shared Recall}}{\left[\frac{\text{Shared List A-1 Recall} + \text{Unshared List A-1 Recall}}{2}\right]}$$

$$\text{Release from PI} = \frac{\left[\frac{\text{Shared List A-1 Recall} + \text{Unshared List A-1 Recall}}{2}\right] - \text{List B Unshared Recall}}{\left[\frac{\text{Shared List A-1 Recall} + \text{Unshared List A-1 Recall}}{2}\right]}$$

$$\text{Build-up of RI} = \frac{\left[\frac{\text{Shared List A-5 Recall} + \text{Unshared List A-5 Recall}}{2}\right] - \text{Short-Delay Free Recall Shared Recall}}{\left[\frac{\text{Shared List A-5 Recall} + \text{Unshared List A-5 Recall}}{2}\right]}$$

Of note, build-up of PI and build-up of RI scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. In contrast, release from PI scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI.

Chapter 3.

Results

Prior to analysis, all variables of interest were examined for accuracy of data entry, missing values, fit between their distributions and the assumptions of multivariate analysis (e.g., normality, linearity, homogeneity of variance, multicollinearity), and univariate and multivariate outliers in accordance with Tabachnick and Fidell (2007). One FE bipolar patient that was flagged as a univariate outlier on numerous variables of interest was excluded from subsequent data analysis as the patient was deemed to be hypomanic at the time of testing and unable to properly complete several tests. Other outlying data points, in which there was no identifiable reason to exclude the patient, were adjusted by making it contiguous with the next closest value while maintaining its distal ranking in the distribution (Tabachnick & Fidell, 2007). Moreover, the IED total number of errors adjusted distribution was highly positively skewed and was consequently subjected to inverse transformation to maintain the assumption of normality, a procedure consistent with past research employing this task (McKirdy et al., 2009).

Demographic Characteristics

Demographic information for the patient and healthy control samples are presented in Table 3.1. The three groups were equivalent on age, $F(2, 238) = 1.27$, $p = .284$, and ethnicity, χ^2 (4, $N = 237$) = 3.06, $p = .547$. However, the groups were not equivalent on total years of education, $F(2, 238) = 30.02$, $p < .001$, premorbid IQ, $F(2, 237) = 27.10$, $p < .001$, and gender, χ^2 (2, $N = 241$) = 13.03, $p = .001$. Post hoc analyses revealed that the FE schizophrenia sample was significantly less educated than both the healthy control ($p < .001$) and FE bipolar ($p < .001$) samples. Similarly, the FE schizophrenia patients' estimated premorbid IQ was significantly lower than both the

healthy control (p < .001) and FE bipolar (p < .001) samples. There were also disproportionately more males than females in the FE schizophrenia sample than in the healthy control sample, χ^2 (1, N = 177) = 13.03, p < .001, and in the FE bipolar sample, χ^2 (1, N = 136) = 3.89, p = .049. In addition to age and ethnicity, post hoc analyses revealed that the FE bipolar and healthy control samples were equivalent on education (p =.980), estimated premorbid IQ (p = .213), and gender, χ^2 (1, N = 169) = 1.94, p = .163.

Table 3.1. Demographic Characteristics of the Participants.

Variable	FES Patients (N = 72)	FEB Patients (N = 64)	Healthy Controls (N = 105)	Group Comparisons
Age (years)	21.40 (6.29)	22.66 (4.58)	22.87 (6.49)	*ns*
Gender (% male)	66.7	50.0	39.0	p<.01; gender difference between FES & HC and between FES & FEB; FEB = HC
Education (years)	11.29 (1.76)	13.31 (2.30)	13.44 (2.25)	p<.001; FES < FEB & HC; FEB = HC
North American Adult Reading Test (Premorbid IQ)[a]	99.78 (8.21)	105.95 (6.88)	107.91 (6.92)	p<.001; FES < FEB & HC; FEB = HC
Ethnicity (%)[b]				*ns*
Caucasian	72.9	76.2	65.4	
Asian	18.6	17.5	26.9	
Other	8.6	6.3	7.7	

Note. Figures indicate mean (*SD*) unless otherwise specified. Group comparisons based on One-Way ANOVA and Chi-square analyses. FES = first episode schizophrenia; FEB = first episode bipolar; HC = healthy controls.

[a]Premorbid IQ score missing for one healthy control.

[b]Ethnicity data were missing for two schizophrenia patients, one bipolar patient, and one healthy control.

Creation of Demographically-Matched Comparison Groups

Given that the FE schizophrenia sample was found to have significantly lower estimated premorbid IQ and disproportionately more males than females than both the

healthy control and FE bipolar samples, demographically-matched healthy control and FE bipolar comparison groups were created to which memory interference in the FE schizophrenia sample could be directly compared[10]. Specifically, this was accomplished by sorting the comparison group data (i.e., healthy control or FE bipolar samples, completed separately) based on: 1) gender, and 2) on NAART IQ scores (in descending order), and then sequentially deleting comparison group females with the highest NAART IQ scores until the FE schizophrenia and comparison group samples were matched on gender ($p > .10$). Then, deletion of comparison group cases continued by alternating between the sequential deletion of females with the highest NAART IQ scores and males with the highest NAART IQ scores until the FE schizophrenia and comparison group samples were additionally matched on estimated premorbid IQ ($p > .10$)[11, 12]. Demographic information for the FE schizophrenia and demographically-matched comparison groups are presented in Table 3.2.

Of note, the rationale for deleting only FE bipolar and healthy control data when creating demographically-matched groups was to preserve the representativeness and generalizability of findings in the geographically-represented FE schizophrenia sample to the catchment area population, as this was the primary group of interest. The purpose of including a FE bipolar sample was to evaluate the specificity of verbal memory

[10] Due to a violation of the Analysis of Covariance (ANCOVA) homogeneity of regression slopes assumption, it was not appropriate to enter the NAART IQ score as a covariate in the memory interference analyses.

[11] An attempt was made to match groups on estimated premorbid IQ only (with the intention of adding Gender as a between-subjects factor in the memory interference analyses model), however, this approach did not increase the sample size of the matched comparison groups and thus the approach of matching groups on both variables was chosen to simplify data analysis.

[12] Given that schizophrenia patients have been previously shown to have lower premorbid IQs than bipolar patients in the real world (e.g., Depp et al., 2007), one could argue that correcting for such a difference might be viewed as overcorrecting. However, exploratory analyses revealed that NAART IQ was not significantly correlated with any of the interference scores or the dependent variables in the main model, and thus it is unlikely that the current approach to data analysis was statistically overcorrecting for differences in premorbid IQs. Nevertheless, data were additionally analysed in the follow two ways: 1) by running the main analyses for males and females separately (ignoring differences in premorbid IQ), and 2) by equating the three groups on gender only by randomly deleting females in the FE bipolar and healthy control samples (resulting in *N*s of 60 and 81, respectively) until gender proportions were matched across the three groups. Results of both analyses were similar to those presented below.

interference in FE schizophrenia by comparing their interference effects to other FE patients that differ in their psychiatric diagnosis but who are otherwise similar. This study was not intended to thoroughly evaluate memory interference in "typical" FE bipolar disorder and thus the representativeness and generalizability of findings to this population was not of primary concern.

Table 3.2. Demographic Characteristics of the FE Schizophrenia and Demographically-Matched Comparison Groups.

Variable	FE Schizophrenia Patients (*N* = 72)	Matched Healthy Controls (*N* = 49)	Matched "Low Functioning" FE Bipolar Patients (*N* = 43)	Group Comparisons
Age (years)	21.40 (6.29)	20.63 (5.60)	21.70 (4.17)	*ns*
Gender (% male)	66.7	53.1	55.8	*ns*
Education (years)	11.29 (1.76)	12.55 (2.30)	12.72 (2.13)	*p* <.001; FES< FEB & HC
NAART IQ	99.78 (8.21)	101.47 (4.39)	101.59 (4.85)	*ns*
Ethnicity (%)[a]				*ns*
Caucasian	72.9	55.6	76.3	
Asian	18.6	35.6	15.8	
Other	8.6	8.9	7.9	

Note. Figures indicate mean (*SD*) unless otherwise specified. Group comparisons based on One-Way ANOVA and Chi-square analyses. FE = first episode; NAART = North American Adult Reading Test. For all *ns* results, $p > .10$.

[a]Ethnicity data were missing for two schizophrenia patients, one bipolar patient, and one healthy control.

Clinical Characteristics

The reader is referred to Table 3.3 for a summary of the clinical characteristics of the patient samples. The FE schizophrenia and demographically-matched FE bipolar samples were equivalent on age at onset of initial psychotic or mood (depressive, hypomanic, or manic) symptoms, $t(105) = -1.18$, $p = .240$, age at first psychotic or manic episode, $t(113) = -0.27$, $p = .785$, time since initial symptoms of illness, $t(105) = 0.53$, $p = .595$, percentage on antipsychotics, χ^2 (1, $N = 114$) = 1.09, $p = .297$, chlorpromazine equivalents, $U = 1250.0$, $p = .146$, percentage on anxiolytics, χ^2 (1, $N = 114$) = 0.08, $p =$

.777, percentage with comorbid DSM-IV alcohol abuse, χ^2 (1, N = 112) = 0.20, p = .654, percentage with comorbid DSM-IV marijuana abuse, χ^2 (1, N = 115) = 1.33, p = .249, and percentage with comorbid polysubstance abuse, χ^2 (1, N = 112) = 0.31, p = .577.

Table 3.3. Clinical Characteristics of the Patient Samples.

Variable	FE Schizophrenia (N = 72)	Unmatched FE Bipolar (N = 64)	Matched FE Bipolar (N = 43)
Diagnosis (%)			
Schizophrenia	75.0		
Schizoaffective	25.0		
Age of illness onset (years)[a,b]	18.97 (5.40)	20.59 (5.27)†	20.24 (5.30)
Age at FE (psychotic or manic; years)	21.40 (6.29)	22.66 (4.58)	21.70 (4.17)
Time since initial symptoms (years)[b]	2.28 (3.96)	2.30 (3.36)	1.87 (3.10)
History of depressive episodes (%)[c]	23.43	49.21**	50.00**
Number of previous depressive episodes (*Mdn,* IQR)[d]		0.00 (0.00-2.00)	0.00 (0.00-2.00)
History of hypomanic episodes (%)[e]		17.20	14.00
Number of previous hypomanic episodes (*Mdn,* IQR)[e]		0.00 (0.00-0.00)	0.00 (0.00-0.00)
Symptom Rating Scales			
Brief Psychiatric Rating Scale[f]	43.06 (8.31)	24.33 (8.51)***	25.02 (9.84)***
Positive and Negative Syndrome Scale			
Positive symptoms	20.51 (6.06)		
Negative symptoms	19.86 (6.14)		
Disorganization symptoms	25.22 (6.17)		
Total score	75.08 (15.18)		
Young Mania Rating Scale (*Mdn,* IQR)[e]		0.00 (0.00-2.00)	0.00 (0.00-2.00)
Hamilton Depression Rating Scale (*Mdn,* IQR)[e]		3.00 (0.00-7.00)	3.00 (0.00-7.75)
Medications[g]			
Time on psychotropics (days; *Mdn,* IQR)	31.0 (0.0-59.0)	57.5 (27.5-86.3)**	60.0 (27.0-85.0)**

Antipsychotics (%)	67.61	78.10	76.74
CPZ equivalents (*Mdn,* IQR)	44.4 (0.0-88.9)	66.7 (7.1-114.3)	86.5 (5.4-119.1)
Mood Stabilizers (%)	0.06	78.13***	76.74***
Lithium (%)	0.03	39.06***	39.53***
Lithium dose (mg)		349.22 (454.39)	373.26 (479.25)
Divalproex (%)	0.03	43.75***	44.19***
Divalproex (mg)		466.80 (581.73)	514.54 (630.46)
Antidepressants (%)	18.31	4.69*	4.65*
Anxiolytics (%)	8.45	6.25	6.98
Substance Abuse (%)[h]			
Alcohol Abuse	7.14	9.68	9.52
Lifetime Alcohol Abuse	47.14	19.35**	19.05**
Marijuana Abuse	45.83	31.75†	34.88
Other Drug Abuse	29.17	7.94**	6.98**
Polysubstance Abuse	15.71	12.90	11.90

Note. Figures indicate mean (*SD*) unless otherwise specified. Group comparisons based on 2-tailed Independent Samples *t*-tests, Mann-Whitney U test, or Chi-square analyses. FE = first episode; *Mdn* = median; IQR = interquartile range; CPZ = chlorpromazine.

† $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$; all other *p*-values >.10.

[a]Age of illness onset is defined as the age in which patients begin to experience their first psychosis or mood (depressive, hypomanic, or manic) symptoms.

[b]Missing data for four schizophrenia patients and five bipolar patients.

[c]Missing data for eight schizophrenia patients and one bipolar patient.

[d]Missing data for five bipolar patients.

[e]Missing data for eight bipolar patients.

[f]Missing data for one bipolar patient.

[g]Missing data for one schizophrenia patient.

[h]Missing data for two schizophrenia patients and two bipolar patients.

However, the FE schizophrenia sample was more psychotic than the matched FE bipolar sample, $t(113) = 10.51$, $p < .001$[13], and a greater percentage of them were

[13] This difference remained significant when comparing FE matched samples whose symptom ratings were obtained within two weeks, $t(69) = 7.04$, $p < .001$, and one week, $t(38) = 7.67$, $p < .001$, of their cognitive assessment.

taking antidepressant medication, χ^2 (1, N = 114) = 4.37, p = .037, had a lifetime DSM-IV diagnosis of alcohol abuse, χ^2 (1, N = 112) = 8.93, p = .003, and/or current comorbid DSM-IV drug abuse, χ^2 (1, N =115) = 8.03, p = .005. Relative to the matched FE bipolar sample, a lower percentage of FE schizophrenia patients had a history of depressive episodes, χ^2 (1, N = 106) = 7.98, p = .005, fewer of them were being treated with mood stabilizers, χ^2 (1, N = 114) = 61.77, p < .001, and they had been receiving psychotropic medication (i.e., antipsychotic and/or mood stabilizer) for a shorter duration of time, U = 980.0, p = .004.

Cognitive Measures

Table 3.4 shows the group differences in general intellectual abilities, working memory/executive functioning, and verbal learning and memory. As expected, FE schizophrenia patients performed worse than demographically-matched healthy controls on most cognitive variables, with the exception of similar serial clustering and number of repetitions on the CVLT-II. Demographically-matched FE bipolar patients also performed worse than healthy controls on the majority of cognitive variables, including those measuring working memory, verbal fluency, set-shifting ability, and verbal learning and memory. Moreover, the matched FE bipolar patients' performance was often intermediate to that of patients with FE schizophrenia and of healthy controls. Specifically, patients with FE schizophrenia had lower intellectual abilities, working memory, set-shifting ability, and verbal learning than matched patients with FE bipolar disorder, but similar verbal fluency and delayed verbal recall. The reader is also referred to Appendix A for the participants' standardized scores correcting for age (and education when available) for the established neuropsychological measures administered.

Table 3.4. Performance on Cognitive Measures.

Variable	FES[a] (*N* = 72)	Unmatched FEB[b] (*N* = 64)	Unmatched HC[c] (*N* = 105)	Unmatched Comparisons	Matched FEB[b] (*N* = 43)	Matched HC[c] (*N* = 49)	Matched Comparisons
K-BIT							
Composite IQ	94.32 (10.23)	104.41 (9.84)	107.70 (9.63)	a<bc*,b<c†	100.81 (8.81)	104.15 (9.30)	a<bc*, b=c
Vocabulary	91.72 (10.21)	100.65 (10.83)	105.11 (10.83)	a<b<c*	96.37 (9.52)	99.88 (10.37)	a<bc*, b=c
Matrices	98.10 (11.65)	107.43 (10.37)	108.73 (9.92)	a<bc*, b=c	105.30 (10.20)	107.71 (11.05)	a<bc*, b=c
COWAT	33.58 (10.31)	37.23 (8.82)	41.91 (10.58)	ab<c*, a<b†	36.28 (9.53)	41.55 (11.58)	ab<c*, a=b
LNS	8.68 (2.42)	10.77 (2.45)	12.01 (2.49)	a<b<c*	10.21 (2.35)	11.49 (2.41)	a<b<c*
IED Errors (*Mdn*, IQR)[a]	27.50 (13.25-59.00)	13.00 (10.00-44.00)	11.00 (9.00-20.00)	a>b>c*	14.50 (11.75-45.75)	12.00 (9.25-21.75)	a>b>c*
CVLT-II							
Trial 1	5.33 (1.79)	6.69 (1.94)	7.44 (2.22)	a<bc*, b<c†	6.33 (1.87)	7.27 (2.23)	a<bc*, b<c†
Trial 5	10.68 (2.68)	12.27 (2.24)	14.08 (1.84)	a<b<c*	11.77 (2.27)	13.96 (1.88)	ab<c*, a<b†
Trials 1-5	43.97 (9.76)	52.06 (10.19)	58.97 (8.84)	a<b<c*	49.81 (10.39)	58.37 (9.12)	a<b<c*
List B	4.88 (1.82)	5.72 (1.80)	6.87 (2.21)	a<b<c*	5.53 (1.82)	6.67 (2.49)	ab<c*, a=b
SDFR	9.33 (3.03)	10.66 (3.00)	12.99 (2.39)	a<b<c*	10.02 (3.01)	12.84 (2.32)	ab<c*, a=b
SDCR	10.04 (2.74)	11.27 (2.93)	13.28 (2.19)	a<b<c*	10.58 (3.07)	13.04 (2.13)	ab<c*, a=b
LDFR	9.36 (3.14)	11.00 (3.10)	13.26 (2.49)	a<b<c*	10.47 (3.33)	13.20 (2.57)	ab<c*, a=b
LDCR	10.11 (2.87)	11.48 (3.01)	13.46 (2.22)	a<b<c*	10.74 (3.17)	13.37 (2.17)	ab<c*, a=b
Sem. Clustering	0.06 (0.97)	0.76 (1.66)	1.95 (2.38)	a<b<c*	0.73 (1.54)	1.74 (2.30)	a<b<c*
Serial Clustering	1.01 (1.12)	0.93 (1.12)	0.66 (1.10)	*ns*	0.78 (0.97)	0.64 (1.17)	*ns*
Primacy Recall	31.28 (7.48)	28.67 (5.15)	28.55 (3.51)	a>c*, a>b†, b=c	28.86 (5.85)	28.18 (3.36)	a>c*, a=b; b=c

Middle Recall	39.14 (8.46)	44.80 (6.65)	44.63 (5.63)	a<bc*, b=c	44.49 (7.11)	44.90 (6.04)	a<bc*, b=c
Recency Recall	29.60 (7.87)	26.66 (5.89)	27.05 (4.25)	a>bc*, b=c	26.72 (6.10)	26.94 (4.48)	a>bc*, b=c
Learning Slope	1.27 (0.60)	1.31 (0.47)	1.59 (0.60)	ab<c*, a=b	1.28 (0.47)	1.63 (0.60)	ab<c*, a=b
Recall Consistency	79.25 (10.07)	81.63 (9.91)	89.28 (6.98)	ab<c*, a=b	80.16 (9.58)	89.02 (6.80)	ab<c*, a=b
Repetitions (*Mdn*, IQR)	4.00 (2.00-7.00)	6.00 (3.00-10.00)	5.00 (3.00-9.00)	*ns*	5.00 (3.00-10.00)	5.00 (3.00-10.50)	*ns*
Intrusions (*Mdn*, IQR)	3.00 (1.00-5.75)	3.00 (1.00-6.00)	1.00 (0.00-3.50)	ab>c*, a=b	4.00 (2.00-8.00)	1.00 (0.00-5.00)	b>c*, a>c†; a=b
Across-List Intrusions (*Mdn*, IQR)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	ab>c*, a=b	0.00 (0.00-1.00)	0.00 (0.00-0.00)	ab<c*, a=b
Recognition (*Mdn*, IQR)	2.70 (2.20-3.70)	3.30 (2.70-3.70)	3.70 (3.40-4.00)	a<b<c*	3.00 (2.00-3.70)	4.00 (3.40-4.00)	ab<c*, a=b

Note. Test performance is presented as raw scores with the exception of the K-BIT (Kaufman Brief Intelligence Test), which is presented as standard scores. Figures indicate the mean (*SD*) unless otherwise specified. Median scores were presented in cases where distributions were significantly skewed. Group comparisons were based on One-Way ANOVAs or non-parametric Independent Samples Kruskal-Wallis *H* tests (when the assumption of normality was violated). FES = first episode schizophrenia; FEB = first episode bipolar; HC = healthy controls; LNS = Letter-Number Sequencing; COWAT = Controlled Oral Word Association Test; IED = Intra-Extra Dimensional Set Shifting Total Errors Adjusted; *Mdn* = median; IQR = interquartile range; CVLT-II = California Verbal Learning Test-II; SDFR = Short Delay Free Recall; SDCR = Short Delay Cued Recall; LDFR = Long Delay Free Recall; LDCR = Long Delay Cued Recall.

† $p < .10$; * $p < .05$; all other p-values >.10; a = schizophrenia; b = bipolar; c = controls.

[a]Missing data for one bipolar patient and one healthy control.

Memory Interference Analyses

The first objective of the present study was to foster a better understanding of the extent to which schizophrenia patients exhibit abnormal verbal memory interference at illness onset. Given past findings of attenuated release from PI and increased build-up of RI in chronic patients with schizophrenia, the current results would help to clarify the extent to which abnormal memory interference is an early manifestation that is central to the disorder rather than a secondary consequence of further illness progression, repeated psychotic episodes, and/or ongoing antipsychotic treatment. The second study objective was to elucidate the extent to which increased susceptibility to interference was unique to FE schizophrenia versus a characteristic of early psychiatric illness in general.

To evaluate these two objectives, PI effects were examined using a 2 x 2 x 3 ANOVA with List (weighted average List A Trial 1, List B) and Category (shared, unshared) as the within-subject factors, Group (FE schizophrenia, matched "low functioning" FE bipolar, matched healthy controls) as the between-subjects factor, and recall accuracy as the dependent variable. Critical findings evaluating the hypothesis that FE schizophrenia patients have reduced release from PI would be demonstrated by a significant List x Category x Group interaction showing attenuated improvement in recall of unshared items from List A to List B in FE schizophrenia patients relative to healthy controls, with performance in the FE bipolar patients expected to fall between that of FE schizophrenia patients and healthy controls.

Similarly, RI effects were examined using a 2 x 2 x 3 ANOVA with List (weighted average List A Trial 5, Short-Delay Free Recall) and Category (shared, unshared) as the within-subject factors, Group (FE schizophrenia, matched "low functioning" FE bipolar, matched healthy controls) as the between-subjects factor, and recall accuracy as the dependent variable[14]. Critical findings evaluating the hypothesis that FE schizophrenia patients have greater build up of RI for shared vs. unshared items would be

[14] The absence of a CVLT-II form effect and its interactions with PI and RI interference effects was verified (all *p*-values > .10), and the order term was dropped from all subsequent analyses.

demonstrated by a significant List x Category x Group interaction showing a relatively greater decline of shared items from List A Trial 5 to List A Short-Delay Free Recall in FE schizophrenia patients relative to healthy controls, with performance in FE bipolar patients expected to fall in between that of FE schizophrenia patients and healthy controls.

An attempt was made to additionally explore group differences in the number of intrusion errors reported from the competing list on the PI and RI trials (i.e., incorrectly recalling List A words on the List B trial for PI, and incorrectly recalling List B words on the Short-Delay Free Recall trial for RI). However, this could not be reliably examined as there were too few individuals in all groups with such intrusion errors on the PI and RI trials. Specifically, on the PI trial, only five schizophrenia patients, two bipolar patients, and three healthy controls made intrusion errors from the competing list, and on the RI trial, only four schizophrenia patients, six bipolar patients, and one healthy control made intrusion errors from the competing list.

Proactive Interference Effects

The obtained means and standard deviations for shared and unshared items recalled on the relevant PI word list trials of the CVLT-II for FE schizophrenia patients, matched "low functioning" FE bipolar patients, and matched healthy controls are presented in Table 3.5. Results of the main analyses revealed a significant main effect of List, $F(1, 161) = 13.85$, $p < .001$, indicating that participants recalled more items on List A, Trial 1 ($M = 3.15$, $SD = 1.00$) than on List B ($M = 2.85$, $SD = 1.05$), which did not differ between groups (List x Group interaction, $F(2, 161) = 0.35$, $p = .706$). The main effect of List was qualified by a significant List x Category interaction, $F(1, 161) = 26.66$, $p < .001$, which demonstrated build-up of PI and release from PI in participants. Specifically, recall of shared items decreased by 18.5% from List A, Trial 1 ($M = 3.35$, $SD = 1.08$) to List B ($M = 2.73$, $SD = 1.24$), $F(1, 163) = 33.83$, $p < .001$ (demonstrating build-up of PI), whereas recall of unshared items by contrast remained largely unchanged from List A, Trial 1 ($M = 2.82$, $SD = 1.11$) to List B ($M = 2.86$, $SD = 1.46$), $F(1, 163) = 0.14$, $p = .713$ (demonstrating release from PI; see Figure 3.1). Moreover, while participants recalled relatively more shared items than unshared items on List A, Trial 1, $F(1, 163) = 123.98$, $p < .001$, this differential recall in shared and unshared items disappeared on List B, $F(1,$

163) = 1.13, p = .290. Of particular interest, however, FE schizophrenia patients demonstrated similar build-up of PI and release from PI compared to matched healthy controls and matched "low functioning" FE bipolar patients, as evidenced by a non-significant List x Category x Group interaction, F(2, 161) = 1.24, p = .292. In other words, while the FE schizophrenia patients demonstrated the expected normal build-up of PI, they did not demonstrate the expected reduced release from PI relative to matched healthy controls.

Table 3.5. Mean (*SD*) of Items Recalled on Proactive Interference Trials for First Episode Schizophrenia Patients, Matched "Low Functioning" First Episode Bipolar Patients, and Matched Healthy Controls.

	Shared Items	Unshared Items	Mean Combined Items
FE Schizophrenia (*N* = 72)			
List A, Trial 1	2.94 (0.98)	2.39 (0.91)	2.67 (0.90)
List B	2.50 (1.08)	2.37 (1.34)	2.44 (0.91)
Mean Combined Trials	2.72 (0.80)	2.38 (0.94)	2.55 (0.77)
Matched FE Bipolar (*N* = 43)			
List A, Trial 1	3.40 (0.96)	2.92 (1.02)	3.16 (0.94)
List B	2.58 (1.24)	2.95 (1.21)	2.78 (0.91)
Mean Combined Trials	2.99 (0.91)	2.94 (0.95)	2.96 (0.80)
Matched Healthy Controls (*N* = 49)			
List A, Trial 1	3.90 (1.08)	3.37 (1.21)	3.63 (1.11)
List B	3.18 (1.35)	3.49 (1.60)	3.34 (1.24)
Mean Combined Trials	3.54 (0.94)	3.43 (1.24)	3.49 (1.01)

Note. FE = first episode.

In addition to the main analyses of interest, results revealed a significant main effect for Group, $F(2, 161) = 17.34$, $p < .001$. Bonferroni corrections were applied to post hoc analyses so that the probability of making a Type I error would be maintained at 0.05, and thus the significance level was subsequently adjusted to $p = .017$. Although post hoc analyses revealed superior overall recall in matched healthy controls compared to both FE schizophrenia patients (p <.001) and FE bipolar patients ($p = .011$), differences in recall between the FE samples did not meet the Bonferroni-corrected

significance level (p = .036). A significant main effect of Category indicated that participants recalled more shared (M = 3.08, SD = 0.90) than unshared (M = 2.92, SD = 1.06) items overall, $F(1, 161) = 5.79$, p = .017, which did not differ between groups (Category x Group interaction, $F(2, 161) = 1.72$, p = .182) [15].

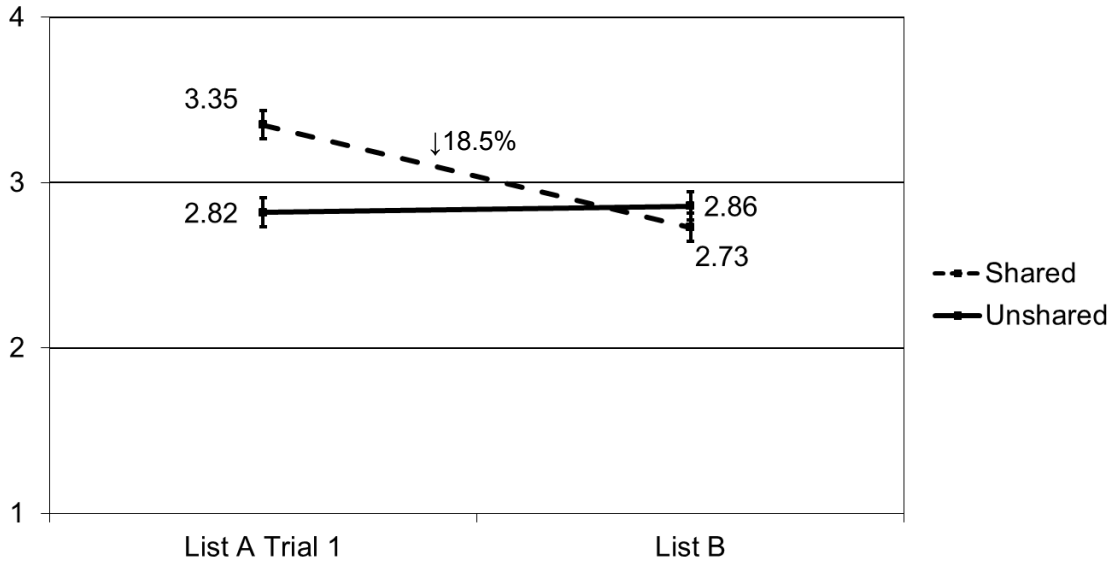

Figure 3.1. Build-Up of Proactive Interference and Release from Proactive Interference in Participants (N = 164).

Note. Figure data points denote mean items recalled with standard error bars.

Retroactive Interference Effects

The obtained means and standard deviations for shared and unshared items recalled on the relevant RI word list trials of the CVLT-II for FE schizophrenia patients, matched "low functioning" FE bipolar patients, and matched healthy controls are presented in Table 3.6. Results of the main analyses revealed a significant main effect of List, $F(1, 161) = 92.02$, $p < .001$, indicating that participants recalled more items on List A, Trial 5 (M = 6.07, SD = 1.20) than on Short-Delay Free Recall (M = 5.37, SD = 1.45).

[15] Results similarly revealed no group differences in build-up of PI and release from PI when relative individual difference scores for the three groups were compared using One-Way ANOVA (p-values >.10).

Table 3.6. Mean (*SD*) of Items Recalled on Retroactive Interference Trials for First Episode Schizophrenia Patients, Matched "Low Functioning" First Episode Bipolar Patients, and Matched Healthy Controls.

	Shared Items	Unshared Items	Mean Combined Items
FE Schizophrenia (*N* = 72)			
List A, Trial 5	5.87 (1.36)	4.81 (1.52)	5.34 (1.34)
SDFR	4.89 (1.68)	4.44 (1.78)	4.67 (1.51)
Mean Combined Trials	5.38 (1.37)	4.63 (1.54)	5.00 (1.34)
Matched FE Bipolar (*N* = 43)			
List A, Trial 5	6.34 (1.21)	5.42 (1.32)	5.88 (1.14)
SDFR	5.26 (1.54)	4.77 (1.96)	5.01 (1.51)
Mean Combined Trials	5.80 (1.24)	5.09 (1.52)	5.45 (1.25)
Matched Healthy Controls (*N* = 49)			
List A, Trial 5	7.52 (0.92)	6.44 (1.28)	6.98 (0.94)
SDFR	6.69 (1.28)	6.14 (1.58)	6.42 (1.16)
Mean Combined Trials	7.11 (0.99)	6.29 (1.30)	6.70 (0.99)

Note. FE = first episode; SDFR = Short-Delay Free Recall.

The main effect of List was qualified by a significant List x Category interaction, $F(1, 161) = 16.10$, $p < .001$, which demonstrated differential build-up of RI for shared and unshared items from List A, Trial 5 to Short-Delay Free Recall (see Figure 3.2). Specifically, recall of shared items decreased by 14.9% from List A, Trial 5 ($M = 6.49$, $SD = 1.39$) to Short-Delay Free Recall ($M = 5.52$, $SD = 1.70$), $F(1, 163) = 104.40$, $p < .001$, whereas recall of unshared items decreased by only 7.7% from List A, Trial 5 ($M = 5.46$, $SD = 1.55$) to Short-Delay Free Recall ($M = 5.04$, $SD = 1.91$), $F(1, 163) = 18.55$, $p < .001$. In contrast to the main hypotheses, however, FE schizophrenia patients demonstrated similar build-up of RI for shared vs. unshared items compared to matched healthy controls and matched "low functioning" FE bipolar patients, as evidenced by a non-significant List x Category x Group interaction, $F(1, 161) = 0.17$, $p = .842$. In other words, FE schizophrenia patients did not demonstrate relatively greater build-up of RI for shared vs. unshared items than matched healthy controls. They also did not demonstrate relatively greater build-up of RI than matched healthy controls when shared

and unshared items were combined (i.e., List x Group interaction, $F(2, 161) = 1.33$, $p = .268$).

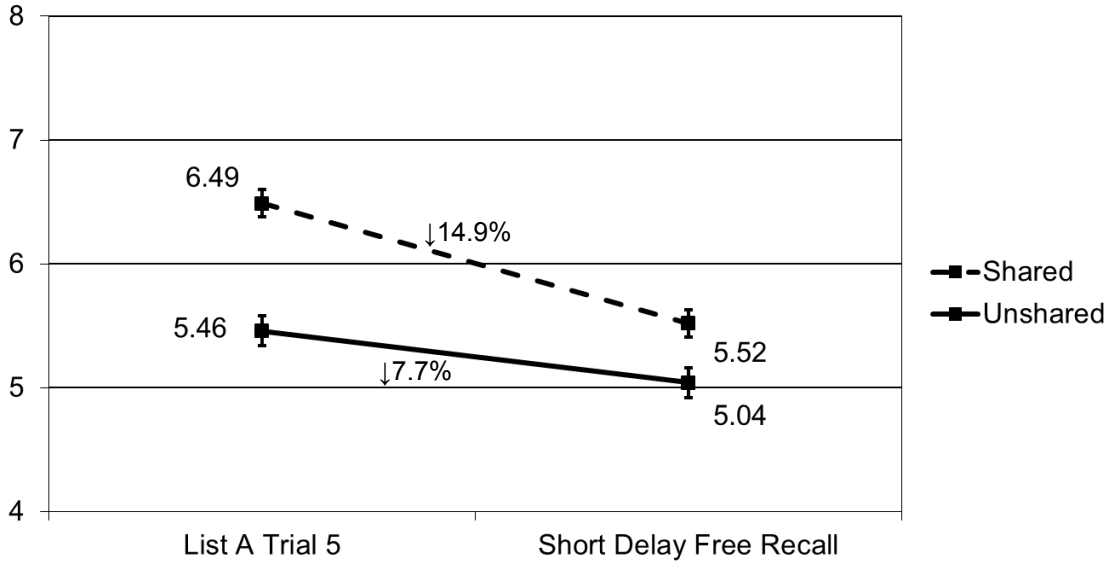

Figure 3.2. Differential Build-Up of Retroactive Interference for Shared and Unshared Category Items in Participants (*N* = 164).

Note. Figure data points denote mean items recalled with standard error bars.

In addition to the main analyses of interest, results revealed a significant main effect for Group, $F(2, 161) = 28.79$, $p < .001$. Bonferroni corrections were applied resulting in an adjusted significance level of $p = .017$. Post hoc analyses revealed superior overall recall in matched healthy controls compared to both FE schizophrenia patients ($p < .001$) and FE bipolar patients ($p < .001$), with equivalent overall recall in FE samples ($p = .146$). A significant main effect of Category indicated that participants recalled more shared ($M = 6.10$, $SD = 1.27$) than unshared ($M = 5.34$, $SD = 1.50$) items overall, $F(1, 161) = 64.08$, $p < .001$, which did not differ between groups (Category x Group interaction, $F(2, 161) = 0.09$, $p = .912$)[16].

Taken together, results of the current study demonstrated normal release from PI and build-up of RI in FE schizophrenia patients relative to demographically-matched

[16] Results similarly revealed no group differences in build-up of RI when relative individual difference scores for the three groups were compared using One-Way ANOVA (*p*-values >.10).

healthy controls. Results further showed similar interference effects in the FE schizophrenia sample and a "low functioning" demographically-matched FE bipolar comparison subgroup.

Potential Variables Affecting PI and RI in FE Schizophrenia

The third objective of the present study was to identify specific cognitive and clinical correlates of memory interference during the FE of schizophrenia. Such findings would help to clarify which factors, if any, affect the degree to which these patients are susceptible to interference.

Working Memory/Executive Functioning

A series of hierarchical regression analyses were used to evaluate the hypotheses that less release from PI would be associated with greater deficits in cognitive flexibility and that increased build-up of RI would be associated with greater deficits in both cognitive flexibility and verbal fluency in FE schizophrenia patients. Given that results of the main analyses revealed similar verbal memory interference between FE schizophrenia and matched FE bipolar patients, particularly in the context of the numerous other similarities in these populations (e.g., genetics, neuropathological, cognitive, and clinical), the possibility of including matched FE bipolar patients in the multiple regression analyses was considered. The inclusion of this comparison group in the model would have the added benefit of clarifying whether any existing associations between executive functioning and memory interference are unique to FE schizophrenia or are rather present in demographically-similar FE patients with a different psychiatric diagnosis. In contrast, the inclusion of the matched healthy control sample in the model was thought to be less interesting as it would limit the ability to evaluate clinical variables that may contribute to interference and its association with executive functioning.

Prior to analyses, zero-order correlations between the dependent variables (i.e., relative individual difference scores for build-up of PI, release from PI, and build-up of RI) and background variables of interest were computed for each FE group (separately) to identify demographic and clinical predictors of interference. Given that the FE groups

differed in their sample sizes (thus differentially impacting *p*-values), background variables were required to predict at least 5% of the variance for the sample being examined to determine whether they should be included in the regression model. To ensure the appropriateness of including the matched FE bipolar sample in the model, the zero-order correlations between interference scores and clinical variables that were unique to either FE group were first inspected to verify whether there existed any unique predictors that should be included in the regression model but that could not be included as there would be no data available for the other group. Specifically, the following unique clinical variables were examined in FE schizophrenia patients: PANSS Positive, Negative, Disorganization, and Total scores, and in matched FE bipolar patients: YMRS ratings (inverse transformed to improve normality), lithium medication status, lithium dose, divalproex medication status, and divalproex dose. Importantly, no clinical variables unique to either FE sample predicted at least 5% of interference-related variance, and it was thus deemed appropriate to include the matched FE bipolar data in the model.

After combining data from both FE groups, zero-order correlations between interference scores and the following common demographic and clinical variables were examined: age, gender, estimated premorbid IQ, age of illness onset, time since initial symptoms, BPRS Total score, depressive mood rating (BPRS Item 9)[17], duration of time on psychotropic medication (square root transformed), chlorpromazine equivalents (square root transformed), lifetime alcohol abuse, and current marijuana abuse. No variables predicted at least 5% of interference-related variance, and therefore no background variables were included in the following regression model. The reader is referred to Appendix B for the Pearson's Product Moment Correlations between background variables and interference scores in FE patients.

Four independent variables were entered into the model in the following order: Block 1, group (i.e., FE schizophrenia patients, matched FE bipolar patients); Block 2,

[17] Given that depressive symptoms are common in both FE schizophrenia and FE bipolar disorder, the "depressive mood" ratings from the BPRS was inspected during pre-screening instead of HAM-D depression scores as data for the former variable was available for all patients in both FE samples whereas data for the latter variable was available in only a subset of the matched FE bipolar patients (*N* = 36 out of 43).

(centered) working memory/executive functioning measures (i.e., Letter-Number Sequencing raw score, inverse of IED total errors adjusted, COWAT total words) to determine the relative contribution of each executive function to interference scores; and Block 3, the interactions between working memory/executive functioning measures (centered) and group (i.e., Letter-Number Sequencing raw score x Group, Inverse of IED total errors adjusted x Group, COWAT total words x Group) to determine whether any existing associations between executive functioning performance and interference differ between FE schizophrenia patients and matched FE bipolar patients. The dependent variables were relative individual difference scores for build-up of PI, release from PI, and build-up of RI (calculated as described in the Methods section).

Build-Up of PI. As indicated in Table 3.7, Block 1 accounted for 2.9 % of the variance in verbal memory interference and suggested a trend for a psychiatric diagnosis of FE bipolar disorder to predict greater build-up of PI (sr^2 = .029). None of the executive functioning measures predicted build-up of PI in FE patients[18]. Of note, none of the executive functioning measures predicted build-up of PI in matched healthy controls (all *p*-values >.10).

Release from PI. As per Table 3.8, Block 1 accounted for only 0.2% of the variance in verbal memory interference, indicating that psychiatric diagnosis did not reliably predict release from PI. In contrast, Block 2 accounted for an additional 11.3% of interference-related variance. Although working memory did not predict release from PI (sr^2 = .013), both poorer verbal fluency ability and greater IED errors predicted less release from PI in FE patients (sr^2 = .043 and sr^2 = .039, respectively). Block 3 accounted for only an additional 1.1% of the variance in verbal memory interference, and indicated that both of the latter associations were not moderated by psychiatric

[18] When data for FE schizophrenia patients were analyzed alone, results suggested a trend for mores IED errors to predict greater build-up of PI, Std. β = .219, p=.071.

diagnosis[19]. Of note, none of the executive functioning measures predicted release from PI in matched healthy controls (all *p*-values >.10).

Table 3.7. Predictors of Build-up of Proactive Interference in FE Patients (*N* = 114).

	R^2	$R^2\,\Delta$	*B*	SE *B*	Std. β	sr^2	*p*
Block 1	.029†	.029†					
Group			-.165	.090	-.171	.029	.069†
Block 2	.052	.022					
Group			-.177	.095	-.184	.030	.065†
LNS			.010	.019	.054	.003	.588
IED[a]			-1.754	1.168	-.143	.020	.136
COWAT			-.002	.004	-.033	.001	.734
Block 3	.071	.019					
Group			-.169	.098	-.175	.026	.087†
LNS			-.011	.033	-.061	.001	.728
IED[a]			.534	2.073	.043	.001	.797
COWAT			.004	.008	.087	.002	.628
LNS x Group			.030	.040	.125	.005	.453
IED[a] x Group			-3.280	2.532	-.215	.015	.198
COWAT x Group			-.006	.010	-.109	.003	.532

Note. Build-up of PI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. LNS = Letter-Number Sequencing; IED = Intra-Extra Dimensional Set Shifting; COWAT = Controlled Oral Word Association Test.

[a] Data for IED total errors adjusted was inverse transformed, and therefore increasingly higher scores denote fewer errors whereas lower scores denote a greater number of errors.

† $p < .10$; all other *p*-values >.10.

[19] When data for FE schizophrenia patients were analyzed alone, results similarly revealed an association between worse verbal fluency and less release from PI, Std. $\beta = .240$, $p = .044$. Although the association between greater IED errors and less release from PI was not significant, Std. $\beta = -.119$, $p = .311$, the direction of the effect was consistent with that of the matched FE bipolar patients, and thus this finding emerged when the samples were combined.

Table 3.8. Predictors of Release from Proactive Interference in Participants (*N* = 114).

	R^2	R^2 Δ	*B*	SE *B*	Std. *β*	sr^2	*p*
Block 1	.002	.002					
Group			.050	.103	.046	.002	.625
Block 2	.115	.113**					
Group			-.059	.104	-.054	.003	.571
LNS			-.026	.020	-.122	.013	.207
IED[a]			-2.786	1.277	-.200	.039	.031*
COWAT			-.011	.005	-.213	.043	.024*
Block 3	.126	.011*					
Group			-.069	.107	-.063	.003	.524
LNS			-.022	.036	-.103	.003	.544
IED[a]			-4.716	2.277	-.339	.035	.041
COWAT			-.010	.009	-.199	.011	.253
LNS x Group			-.006	.044	-.024	.000	.883
IED[a] x Group			3.000	2.781	.174	.010	.283
COWAT x Group			-.003	.011	-.039	.000	.816

Note. Release from PI relative individual interference difference scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI. LNS = Letter-Number Sequencing; IED = Intra-Extra Dimensional Set Shifting; COWAT = Controlled Oral Word Association Test.

[a] Data for IED total errors adjusted was inverse transformed, and therefore increasingly higher scores denote fewer errors whereas lower scores denote a greater number of errors.

* $p < .05$; ** $p < .01$; all other *p*-values >.10.

Build-Up of RI. Block 1 accounted for only 0.1% of the variance in verbal memory interference, indicating that psychiatric diagnosis did not reliably predict build-up of RI (Std. β = -.083, $p = .381$). This block was subsequently dropped from the model to improve predictive power due to a near marginal finding (inverse IED errors: Std. β = .150, $p = .114$). After dropping the Group variable from the model, results suggested a trend for fewer IED errors to predict greater build-up of RI in FE patients ($sr^2 = .027$), as

Table 3.9. Predictors of Build-Up of Retroactive Interference in Participants (*N* = 114).

	R^2	$R^2\,\Delta$	*B*	SE *B*	Std. β	sr^2	*p*
Block 1	.033	.033					
LNS			-.009	.011	-.084	.007	.384
IED[a]			1.217	.702	.164	.027	.086[†]
COWAT			.001	.003	.049	.002	.610
Block 2	.048	.015					
LNS			-.016	.019	-.145	.006	.397
IED[a]			.086	1.214	.012	.000	.945
COWAT			.002	.005	.074	.002	.678
LNS x Group			.011	.024	.076	.002	.645
IED[a] x Group			1.775	1.531	.193	.012	.249
COWAT x Group			-.002	.006	-.046	.001	.794

Note. Build-up of RI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. LNS = Letter-Number Sequencing; IED = Intra-Extra Dimensional Set Shifting; COWAT = Controlled Oral Word Association Test.

[a] Data for IED total errors adjusted was inverse transformed, and therefore increasingly higher scores denote fewer errors whereas lower scores denote a greater number of errors.

[†] $p < .10$; all other *p*-values >.10.

indicated in Table 3.9[20]. This potential association was not moderated by psychiatric diagnosis. Working memory and verbal fluency did not reliably predict verbal memory interference. Of note, fewer IED errors predicted greater build-up of RI in matched healthy controls (Std. β = .332, $p = .019$), indicating that this association was not unique to FE psychiatric illness.

Taken together, poorer executive functioning (specifically, poorer verbal fluency ability and greater IED errors) predicted less release from PI in FE patients, regardless of their psychiatric diagnosis. Results further suggested a trend for fewer IED errors to predict greater build-up of RI in FE patients, regardless of psychiatric diagnosis, which

[20] Findings were similar when data for the FE schizophrenia sample were analyzed alone (inverse IED errors: Std. $\beta = .223$, $p = .067$).

was consistent with findings in matched healthy controls. Executive functioning did not significantly predict build-up of PI.

Clinical Variables of Interest

Given that the majority of psychotic symptom scores were available for only the FE schizophrenia sample (i.e., PANSS Positive, Negative, Disorganization, and Total scores), the following exploratory analyses did not combine these data with that of the matched FE bipolar sample. This approach allowed for a more thorough examination of the symptoms correlates of verbal memory interference in the primary group of interest as the analyses were not limited to the one symptom score available to both patient groups. Nevertheless, it is worth noting that similar results were found when combined data for all FE patients were analyzed on those clinical variables available to both groups (i.e., age of illness onset, time since initial symptoms of illness, BPRS Total score, time on psychotropic medication, and chlorpromazine equivalents).

Symptoms. To explore whether severity of psychiatric symptoms is associated with memory interference in FE schizophrenia patients, Pearson product moment correlations were computed between symptom ratings and relative individual interference difference scores. Bonferroni corrections were applied resulting in an adjusted significance level of $p = .01$. As shown in Table 3.10, results did not reveal any significant associations between psychiatric symptoms and verbal memory interference[21].

Medications. To explore whether the use of antipsychotic medication in FE schizophrenia patients is associated with memory interference, correlations were computed between relative individual interference difference scores and both chlorpromazine equivalents and duration of time on antipsychotic medication. Bonferroni corrections were applied resulting in an adjusted significance level of $p = .025$. As shown

[21] Results were largely unchanged when partial correlations were used to control for the number of days elapsed between cognitive testing and both BPRS and PANSS ratings (all *p*-values > .10).

in Table 3.11, results did not reveal any significant associations between medication variables and verbal memory interference.

Table 3.10. Correlations Between Symptom Ratings and Memory Interference in FE Schizophrenia Patients (*N* = 72).

	Build-up of PI	*p*-value	Release from PI	*p*-value	Build-up of RI	*p*-value
BPRS	0.02	.850	-0.10	.421	-0.03	.779
PANSS						
Positive symptoms	0.14	.229	-0.09	.461	0.06	.599
Negative symptoms	-0.02	.841	0.09	.475	-0.08	.521
Disorganization symptoms	0.03	.833	-0.16	.184	-0.10	.393
Total score	0.03	.832	-0.10	.430	-0.06	.609

Note. Build-up of PI and RI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. In contrast, release from PI scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI. PI = proactive interference; RI = retroactive interference; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale.

All *p*-values = *ns.*

Table 3.11. Correlations Between Antipsychotic Medication Variables and Memory Interference in FE Schizophrenia Patients (*N* = 71).

	Build-up of PI	*p*-value	Release from PI	*p*-value	Build-up of RI	*p*-value
Time on Antipsychotics	0.07	.561	0.06	.625	-0.00	.996
CPZ	0.11	.365	0.18	.139	0.01	.964

Note. Spearman's rho correlations were used due to the abnormal distributions of chlorpromazine equivalents and duration of time on antipsychotic medication. Build-up of PI and RI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. In contrast, release from PI scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI. PI = proactive interference; RI = retroactive interference; CPZ = chlorpromazine equivalents.

All *p*-values = *ns.*

Given the disproportionate number of patients who were not receiving antipsychotic medication, correlations were additionally computed between antipsychotic medication variables and relative interference difference scores while excluding patients who were not receiving antipsychotics (i.e., those patients with medication variable scores of zero). Bonferroni corrections were applied resulting in an adjusted significance level of $p = .025$. As indicated in Table 3.12, chlorpromazine equivalents and duration of time on antipsychotics were again unrelated to verbal memory interference in the FE schizophrenia sample.

Table 3.12. Correlations Between Antipsychotic Medication Variables and Memory Interference for Only Those Schizophrenia Patients Receiving Antipsychotic Medication (*N* = 48).

	Build-up of PI	*p*-value	Release from PI	*p*-value	Build-up of RI	*p*-value
Time on Antipsychotics	0.01	.954	-0.02	.872	0.02	.877
CPZ	0.06	.703	0.10	.488	0.05	.728

Note. Pearson product moment correlations were used as distributions of antipsychotic medication variables were no longer abnormal after removing scores of zero. Build-up of PI and RI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. In contrast, release from PI scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI. PI = proactive interference; RI = retroactive interference; CPZ = chlorpromazine equivalents.
All *p*-values = *ns.*

Other Clinical Variables. While age of onset of initial symptoms of illness was not associated with build-up of PI or release from PI in FE schizophrenia patients (all *r*'s, $p > .10$), there was a trend for earlier age at onset to be associated with greater build-up of RI ($r = -0.21$, $p = .094$). Interference effects were not significantly associated with time since initial symptoms of illness (all *r*'s, $p > .10$). Moreover, there was no significant difference in interference effects between psychotic patients diagnosed with schizophrenia ($N = 54$) and those diagnosed with schizoaffective disorder ($N = 18$; all *t*-tests, $p > .10$).

The Effects of PI and RI on Delayed Verbal Memory in FE Schizophrenia

Multiple regression analyses were used to explore whether greater memory interference significantly contributes to worse delayed verbal recall in FE schizophrenia. As with the executive functioning analyzes, the possibility of including matched FE bipolar patients in these multiple regression analyses was considered as this would have the added benefit of clarifying whether any existing associations between interference and delayed verbal recall are unique to FE schizophrenia or are rather present in demographically-similar FE patients with a different psychiatric diagnosis.

Prior to analyses, zero-order correlations were computed between the dependent variable (i.e., Long-Delay Free Recall trial on the CVLT-II) and background variables of interest to identify demographic and clinical predictors of interference in FE schizophrenia and matched FE bipolar patients (performed separately). Background variables were required to predict at least 5% of the variance for the sample being examined to determine whether they should be included in the regression model. To ensure the appropriateness of including the matched FE bipolar sample in the model, the zero-order correlations between delayed verbal recall and clinical variables of interest that were unique to either FE group were first inspected to verify whether there existed any unique predictors that should be included in the regression model but that could not be included as there would be no data available for the other group. Importantly, no clinical variables unique to either FE sample predicted at least 5% of interference-related variance, and it was thus deemed appropriate to include the matched FE bipolar data in the model.

After combining data from both FE groups, zero-order correlations between delayed verbal recall and common demographic and clinical variables of interest were examined. The reader is referred to Appendix C for the Pearson's Product Moment Correlations between background variables and Long-Delay Free Recall in FE patients. Importantly, overall severity of psychotic symptoms (BPRS Total score) was found to predict at least 5% of interference-related variance.

Subsequently, relevant independent variables were entered into the model in the following order: Block 1, BPRS Total score to control for the severity of overall psychotic symptoms; Block 2, group (i.e., FE schizophrenia patients, matched FE bipolar patients); Block 3, (centered) relative interference difference scores (i.e., build-up of PI, release from PI, and build-up of RI) to determine the relative contribution of each interference score to delayed verbal recall; and Block 4, the interactions between interference scores (centered) and group (i.e., build-up of PI x Group, release from PI x Group, build-up of RI x Group) to determine whether any existing associations between interference and memory recall differ between FE schizophrenia patients and matched FE bipolar patients. Long-Delay Free Recall from the CVLT-II was the dependent variable.

As indicated in Table 3.13, Block 1 accounted for 6.1% of the variance in delayed verbal recall, indicating that more severe psychotic symptoms reliably predicted worse verbal memory. In contrast, Block 2 did not account for any additional memory-related variance, indicating that psychiatric diagnosis did not predict delayed recall. Blocks 3 and 4 accounted for only an additional 2.1% and 1.6% of the variance, respectively, with none of the interference indices or their interactions with psychiatric diagnosis reliably predicting worse long-delay free recall.[22] Of note, none of the interference scores predicted delayed verbal recall in matched healthy controls (all *p*-values >.10).

[22] Findings were similar when data for the FE schizophrenia sample were analyzed alone (all *p*-values >.10 for memory interference predictors).

Table 3.13. Predictors of Long-Delay Free Recall in FE Patients (*N*=115).

	R^2	$R^2\,\Delta$	*B*	SE *B*	Std. β	sr^2	*p*
Block 1	.061**	.061**					
BPRS Total Score			-.064	.024	-.247	.061	.008**
Block 2	.061*	.000					
BPRS Total Score			-.067	.033	-.259	.034	.047*
Group			.111	.859	.017	.000	.897
Block 3	.082†	.021					
BPRS Total Score			-.073	.034	-.280	.039	.033*
Group			.264	.877	.040	.001	.764
Build-Up of PI			.393	.657	.056	.003	.551
Release from PI			-.725	.575	-.118	.013	.210
Build-Up of RI			-.971	1.071	-.084	.007	.366
Block 4	.098	.016					
BPRS Total Score			-.073	.034	-.281	.039	.034*
Group			.178	.887	.027	.000	.842
Build-Up of PI			-.172	1.184	-.025	.000	.885
Release from PI			-.074	1.039	-.012	.000	.943
Build-Up of RI			-2.771	2.239	-.240	.013	.219
Build-Up of PI x Group			.894	1.426	.105	.003	.532
Release from PI x Group			-.947	1.249	-.128	.005	.450
Build-Up of RI x Group			2.355	2.553	.179	.007	.358

Note. Build-up of PI and RI relative individual interference difference scores above zero denote increasingly greater build-up of interference, whereas scores below zero denote less build-up of interference. In contrast, release from PI scores above zero denote attenuated release from PI, whereas scores below zero denote increasingly greater release from PI. BPRS = Brief Psychiatric Rating Scale; PI = proactive interference; RI = retroactive interference.

† $p < .10$; *$p < .05$; **$p < .01$; all other *p*-values >.10

Chapter 4.

Discussion

The Nature of Verbal Memory Interference in FE Schizophrenia

Given that the majority of past studies examining PI and/or RI in schizophrenia have employed chronic samples of patients, the first objective of the present study was to foster a better understanding of the extent to which these patients exhibit abnormal verbal memory interference at illness onset. Importantly, findings would help to clarify the extent to which memory interference is an early manifestation that is central to the disorder rather than a secondary consequence of further illness progression, repeated psychotic episodes, and/or ongoing antipsychotic treatment. Ultimately, these findings would help to elucidate the specific mechanisms that hinder learning and recall of verbal information in schizophrenia, thereby giving insight into potential avenues for early intervention.

As predicted, FE patients with schizophrenia exhibited similar build-up of PI relative to demographically-matched healthy controls. This finding is consistent with the majority of past research demonstrating normal build-up of PI in chronic patients with the disorder (e.g., Moritz et al., 2001; O'Carroll et al., 1993; Paulsen et al., 1995; Torres et al., 2001), as well as the limited research examining build-up of PI at illness onset (Hill et al., 2004; Sitskoorn et al., 2002).

Contrary to predictions, however, FE schizophrenia patients did not demonstrate attenuated release from PI compared to demographically-matched healthy controls. This finding is in contrast to the only other known study examining release from PI in FE schizophrenia patients (Sitskoorn et al., 2002) as these researchers found evidence of reduced release from PI in their sample. It is important to note, however, that while

Sitskoorn et al. (2002)'s study reportedly employed FE schizophrenia patients, they did not specify how long it had been since their sample of patients had been diagnosed with their FE of illness. Their only reference to duration of illness was that patients were excluded if they had been experiencing hallucinations and/or delusions for more than two years. In contrast, the FE patients employed in the current study were required to have experienced their FE of illness within three months of study enrolment. Also of note, 86% (30/35) of their patients were receiving antipsychotic medication while only 67% (48/72) of the current sample of patients was receiving antipsychotic medication, χ^2 (1, N = 107) = 3.96, p = .047. Finally, the current sample of patients had a median antipsychotic medication duration of only 28.5 days (interquartile range = 0.00-56.75). Although Sitskoorn et al. (2002) did not report the duration of antipsychotic medication usage in their sample, they included patients who had been experiencing psychotic symptoms for up to two years, and therefore it seems plausible that their patients may have been treated with antipsychotics for a longer period of time than patients in the current sample. Taken together, it appears quite plausible that the current sample of FE patients was relatively earlier in the course of illness and/or treatment with antipsychotics than the patients employed in Sitskoorn et al.'s (2002) study. As such, it may be the case that Sitskoorn et al.'s (2002) findings of attenuated release from PI in their sample of patients, within the context of the current null results, may reflect secondary effects of illness progression and/or antipsychotic treatment. Such a pattern of findings would imply that vulnerability to memory interference in schizophrenia develops relatively quickly in the early course of illness and/or medication treatment.

Also contrary to predictions, the current study did not find evidence of heightened build-up of RI in FE schizophrenia patients relative to demographically-matched healthy controls. Although these findings are indeed consistent with the only other known study examining build-up of RI in FE schizophrenia patients (Hill et al., 2004), it had been expected that patients would show increased RI in the current study as interference was examined by comparing shared (i.e., semantically related) versus unshared (i.e., semantically unrelated) items on the CVLT-II (Kramer & Delis, 1991) rather than employing a simple difference score as used by Hill et al. (2004). Differential findings were expected because interference is known to be greatest when competing information is semantically similar (Wickens, 1970), and thus abnormal susceptibility to

interference is not always detected when shared and unshared items are combined (Numan et al., 2000). Nevertheless, the fact that the current study also found similar build-up in RI in FE schizophrenia patients relative to matched healthy controls adds further support to the contention that heightened build-up in RI is not present at illness onset.

Taken together, the current findings of normal build-up of PI, release from PI, and build-up of RI in FE schizophrenia patients suggests that verbal memory interference is not an early manifestation that is central to this psychiatric disorder (e.g., an endophenotype). Given past findings of attenuated release from PI (e.g., Kay, 1982; Randolph et al., 1992) and heightened build-up of RI (e.g., Kareken et al., 1996; Sengel et al., 1985; Torres et al., 2001) in chronic patients with schizophrenia, the current results instead suggest that increased susceptibility to memory interference in schizophrenia is more likely attributable to illness progression, repeated psychotic episodes, and/or ongoing antipsychotic treatment. It may therefore be the case that there is a window of opportunity for clinical intervention in the early course of illness to help prevent or minimize the development of abnormal verbal memory interference.

It is also worth noting that interference effects in the current study did not significantly predict worse long-delay free recall in FE patients. In other words, interference from competing information did not reliably contribute to these patients' eventual poor delayed verbal memory. One possibility is that these patients, like the matched healthy controls, were not particularly susceptible to the impact of interference on memory recall because they had normal build-up and release of interference. Thus, the impact of interference on verbal memory recall in schizophrenia patients with attenuated release from PI and/or increased build-up of RI remains unclear. It may be the case that as abnormal release from PI and build-up of RI develop over time, they begin to negatively impact delayed verbal memory. Nevertheless, the current findings suggest that interference from competing information is not a critical determinant of long-term memory at illness onset in schizophrenia.

The Specificity of Verbal Memory Interference in FE Schizophrenia

The second objective of the present study was to elucidate the extent to which increased susceptibility to interference was unique to FE schizophrenia versus a characteristic of early psychiatric illness in general. First-episode bipolar patients were selected as a comparison group as they exhibit notable verbal memory impairment, prefrontal abnormalities, and deficits on tasks that entail prefrontal functioning, which are generally similar to those with schizophrenia, albeit with quantitatively less impairment. Given the implication that intact prefrontal functioning is needed for adequate recall despite interference and that prefrontal functioning appears to be relatively more impaired in FE schizophrenia than in FE bipolar disorder, it was predicted that FE patients with bipolar disorder would exhibit a similar pattern of interference effects that are intermediate to that of FE patients with schizophrenia and healthy controls.

However, as described above, results unexpectedly demonstrated normal verbal memory interference in FE schizophrenia patients relative to demographically-matched healthy controls. Thus, the question of specificity of memory interference in FE schizophrenia becomes less relevant as it assumes abnormal susceptibility to interference in this population. Nevertheless, the main analyses revealed similar interference effects in the FE schizophrenia sample and a "low functioning" FE bipolar comparison subgroup that was created to match groups on estimated premorbid IQ and gender (in addition to age and ethnicity). Although results of subsequent regression analyses suggested the possibility of relatively higher build-up of PI in the matched FE bipolar sample compared to the FE schizophrenia sample, it is important to note that interference effects in these bipolar patients did not significantly differ from that of matched healthy controls, $t(90) = 1.06$, $p = .294$, thus suggesting normal interference in this sample as well.

Cognitive and Clinical Correlates of Memory Interference in FE Schizophrenia

The third objective of the present study was to identify specific cognitive and clinical correlates of memory interference during the FE of schizophrenia. Such findings would help to clarify which factors, if any, affect the degree to which FE schizophrenia patients are susceptible to interference. Ultimately, the identification of such factors is helpful as it would provide insight into potential avenues of early cognitive intervention.

Working Memory/Executive Functioning Correlates

Results of the current study provided some support for an association between poorer executive functioning and greater vulnerability to verbal memory interference following the FE of psychiatric illness. As hypothesized, poorer cognitive flexibility/set shifting was significantly associated with attenuated release from PI. In other words, FE patients who are more cognitively inflexible have greater difficulty shifting to recalling target items from less distracting semantically unrelated categories on the PI trial in order to aid retrieval. This finding is consistent with past research showing this association in chronic patients with schizophrenia (Randolph et al., 1992). Moreover, poorer verbal fluency ability was also associated with attenuated release from PI in FE patients. As previously noted, verbal fluency relies on effortful self-initiation while monitoring and inhibiting inappropriate responding (Henry & Crawford, 2004). It may therefore be the case that poorer verbal fluency in psychiatric patients hinders their ability to self-initiate recall of target items while inhibiting previously presented distracting material during the PI trial. Although lower executive functioning ability did not significantly predict worse memory interference in the matched healthy control sample, the strength of these associations did not differ between FE samples, thus suggesting that they are not unique to FE schizophrenia but are rather characteristic of FE psychiatric illness more generally. These findings additionally lend further support to the contention that prefrontal functioning is a critical determinant of memory interference, as these executive functions are thought to be sensitive to prefrontal functioning.

Nevertheless, it seems plausible that the current samples of FE patients, like healthy controls, may have had sufficiently adequate executive functioning abilities

overall to both shift to recalling target items from less distracting semantically unrelated categories on the PI trial and to self-initiate recall of target items despite interference from distracting material, thereby resulting in normal memory interference scores overall. Although the current sample of FE schizophrenia patients had medium to large set-shifting (*d* = -0.70) and verbal fluency deficits (*d* = -0.74) compared to matched healthy controls, chronic schizophrenia patients typically have even larger set-shifting and verbal fluency deficits that are considered to be among the most powerful and reliable findings of abnormalities in schizophrenia, with meta-analytic effect sizes of *d* = -0.88 (*CI*: *d* = -0.76 to *d* = -1.00) for set-shifting and of *d* = -1.09 (*CI*: *d* = -0.92 to *d* = -1.26) for verbal fluency (Heinrichs, 2004). It may be that worsening set-shifting and verbal fluency over time in these patients contribute to increasingly greater susceptibility to memory interference, culminating in abnormal interference effects later in the course of illness.

Contrary to predictions, however, poorer cognitive flexibility and poorer verbal fluency was not associated with greater build-up of RI in FE patients, despite past findings of such associations in chronic patients with schizophrenia (Torres et al., 2001). In other words, schizophrenia patients in the early course of illness are adequately able to: 1) shift back to recalling previously learned target information on the RI trial after being presented with new interfering material, and 2) fluently verbalize previously learned target items on the RI trial post-interference. In fact, there was even the suggestion of an association between fewer errors on the IED Set Shifting task and greater build-up of RI in FE patients in general, and this association was reliably found in matched healthy controls. Of note, good performance on the latter task would require examinees to sense a change in task requirements and to attend to that change. It may be the case that as people in general are better able to sense and attend to the semantic properties of CVLT-II words (whether it be through conscious attention or unconscious semantic priming), the more difficult it is to retain previously learned information following the learning of semantically similar distracting information.

Taken together, the current findings suggested that, while poorer executive functioning is associated with attenuated release from PI in the FE of psychiatric illness, it is not associated with susceptibility to RI at illness onset. These findings provide at least some support for the contention that memory interference is related to abnormal prefrontal functioning. Nevertheless the lack of association between poorer executive

functioning and greater susceptibility in RI at illness onset is in contrast to previous research demonstrating a detrimental impact of executive functioning deficits on chronic patients' ability to recall target information on the RI trial (Torres et al., 2001). Given previous findings of significantly worse cognitive flexibility and verbal fluency in patients with chronic schizophrenia compared to those in their FE (Braw et al., 2008; Townsend & Norman, 2004), it nevertheless seems plausible that these cognitive abilities may still be sufficiently adequate at illness onset to produce normal interference effects overall. Perhaps abnormal memory interference develops with further deterioration of executive functions as illness burden accumulates over the course of illness.

Clinical Correlates

An exploration of potential clinical correlates of verbal memory interference in FE schizophrenia revealed that interference effects in the current sample did not vary as a function of psychotic symptoms, antipsychotic dose, or length of time on antipsychotic medication. In other words, the current sample of FE schizophrenia patients did not show evidence of abnormal susceptibility to verbal memory interference, and neither their clinical symptom presentation nor their antipsychotic usage appeared to have a detrimental impact on their relatively normal interference susceptibility.

Although the current null finding of a lack of an association between verbal memory interference and antipsychotic medication dosage is consistent with the limited research that has directly examined this relation in schizophrenia (Kay, 1982; Roofeh et al., 2006), it nevertheless seems surprising given previous research linking the deterioration of the frontal lobes to antipsychotic usage (Andreasen, Liu, Ziebell, Vora, & Ho, 2013; Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011; Radua et al., 2012), particularly with typical vs. atypical antipsychotics (Dazzan et al., 2005; Gur, Cowell, et al., 1998; Lieberman et al., 2005; Smieskova et al., 2009; Thompson et al., 2009), even after only two or three months of treatment (Dazzan et al., 2005; Lieberman et al., 2005). One would expect that frontal lobe atrophy related to cumulative antipsychotic usage over time would result in worsening of PI and RI. One possibility may be that schizophrenia patients in the early course of illness are able to sufficiently withstand the detrimental impact of memory interference despite some degree of frontal lobe abnormality (structural and/or functional), but that once a particular threshold of

abnormality is attained, they begin to exhibit disproportionate susceptibility to interference compared to healthy individuals. Given that the current patient sample's median length of medication usage was only one month, it may be the case that a longer length of medication usage, and thus greater frontal lobe abnormality, would be required for these patients to experience abnormal verbal memory interference.

The possibility of a frontal lobe abnormality threshold may underlie the current study's suggestion of an association between earlier age at onset of initial symptoms and greater build-up of RI. Specifically, past research has revealed that schizophrenia patients with an earlier age of onset typically have greater prefrontal atrophy and poorer verbal memory, cognitive flexibility, and verbal fluency (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011; Rajji, Ismail & Mulsant, 2009). It may be that these patients experience an earlier disruption in the maturational processes of the prefrontal cortex that typically occur in adolescence, thus reaching the threshold of frontal lobe abnormality and related disproportionate build-up of RI sooner than patients with a relatively later illness onset. Moreover, a frontal lobe abnormality threshold may further help explain why FE patients with some degree of executive functioning deficits nevertheless exhibit normal interference effects despite evidence of associations between these cognitive abilities and memory interference susceptibility. Likewise, while FE schizophrenia patients appear sufficiently able to withstand the detrimental impact of interference on memory despite certain clinical symptoms that would likely tax their already limited cognitive resources (e.g., auditory hallucinations and thought disorder), it seems plausible that this would become increasingly more difficult once a particular threshold of frontal lobe abnormality is reached. Further clarification of this issue appears warranted in future research.

To summarize, the results of the current study revealed normal verbal memory interference in FE schizophrenia patients despite evidence of attenuated release from PI and greater build-up of RI in chronic patients with the disorder. Although some associations between poorer executive functions and interference emerged in FE patients in general, susceptibility to interference was mostly unrelated to the clinical characteristics of the samples and, importantly, it did not significantly contribute to these patients' eventual poor recall of verbal information. This begs the question: What mechanism(s) underlie verbal memory impairment at illness onset in schizophrenia?

Within the current dataset, poorer semantic clustering of information during learning trials of the CVLT-II, in particular, was significantly associated with worse eventual long-term memory recall in these patients, r = .384, p =.001, accounting for 15% of the variance. This is particularly problematic given that these patients typically experience abnormal activation of semantic networks (see Mohammad & DeLisi, 2013 for a review) and have significant difficulty organizing semantic information (d = -1.02 in the current sample). Although preliminary, these findings may provide useful insight into potential avenues for further study and ultimately direction for early cognitive intervention to improve verbal memory in schizophrenia. Of course, there are likely other factors underlying verbal memory impairment in FE schizophrenia that were not available for direct exploration in the current study (e.g., genetic, neuropathological), and for which clarification in future research would be beneficial.

Limitations

The Use of Previously Ascertained Databases

Data for the current study was drawn from two previously ascertained databases of FE patients, and thus the design of this study was limited to the data obtained and the procedures chosen for the parent studies. While the main measures and procedures of the parent studies were certainly appropriate to address the objectives of the current study, alternative decisions would have nevertheless been made regarding the study's design had original data been collected. Specifically, diagnostic information for the FE schizophrenia and FE bipolar samples would have both been obtained using the same structured interview measure and by the same individual. It is worth noting, however, that all information required to make the DSM-IV diagnoses were nevertheless obtained by each diagnostic measure and thus accurate diagnoses would have been made regardless of the measure employed or the trained individual that completed them. The current study would have also required that the psychosis ratings be obtained consistently in proximity to the date of cognitive testing, though it seems unlikely that this would have produced significant associations between psychosis ratings and interference effects (as discussed below). In addition, the current study would have employed the same alternate form of the CVLT-II when testing all participants, however

the use of alternate forms in the parent studies is unlikely to have accounted for the current findings given that the forms are psychometrically comparable (Delis et al., 2000) and because the CVLT-II form used did not interact with interference effects in the current analyses. Finally, the current study would have included a measure of temporal order judgment, as this executive function has been previously shown to be related to build-up of RI in chronic schizophrenia patients (Torres et al., 2001). Without the inclusion of such a measure, the present study could not assess the possibility that deficits in temporal order judgment predict abnormal memory interference in FE schizophrenia.

Sample Size and Characteristics

The FE schizophrenia patients employed in the current study had significantly lower estimated premorbid IQ than both the FE bipolar patients and healthy controls, a finding consistent with previous research and which appears to reflect real-world differences between these populations (e.g., Daban et al., 2006; Depp et al., 2007; Glahn et al., 2006). Although not ideal, the creation of demographically-matched comparison subgroups permitted a direct comparison between groups in order to clarify the nature and specificity of interference effects in FE schizophrenia, as this group difference could not be dealt with statistically (as described in Footnote 10). It is unlikely that matching groups on premorbid IQ resulted in statistical overcorrection given that NAART IQ was not significantly correlated with the interference scores or with any of the dependent variables in the main model. While this matching procedure decreased the size of the FE bipolar and healthy control samples, thereby reducing statistical power, it is important to note that the null findings for the main question of interest regarding that nature of memory interference in FE schizophrenia do not appear to be the result of insufficient power (build-up of PI: d = 0.14; release from PI: d = -0.08; build-up of RI: d = -0.10).

Most importantly, the composition of the geographically-represented FE schizophrenia sample was unchanged, and thus findings for the primary group of interest should be representative of the catchment area population. As this study was not intended to thoroughly evaluate memory interference in "typical" FE bipolar disorder, maintaining the representativeness and generalizability of the FE bipolar sample was

less of a concern. Rather, the inclusion of this sample for the purpose of evaluating the specificity of interference in FE schizophrenia was accomplished by the current study methods.

Although the three matched samples did not significantly differ on ethnicity, the ethnic composition of the FE schizophrenia sample was 72.9% Caucasian vs. 18.6% Asian and the matched FE bipolar sample was similarly 76.3% Caucasian vs. 15.8% Asian, whereas the matched healthy control sample was 55.6% Caucasian vs. 35.6% Asian. While the relative proportion of Caucasian vs. Asian participants in the FE samples compared to the healthy control sample may be questioned, it is worth noting that the impact of ethnicity on the current findings was investigated and was subsequently considered to be non-contributory. Specifically, relative individual difference scores for build-up of PI, release from PI, and build-up of RI did not significantly differ between ethnic groups, demonstrating similar susceptibility to memory interference (all *p*-values >.10). Moreover, when ethnicity was added as a between-subjects factor in the main ANOVA model evaluating differences in PI and RI between the three groups, results were largely unchanged and ethnicity did not interact with other variables in the model.

Reliability of Interference Scores

Although reliability coefficients for the trials that make up the interference effects are adequate (Delis et al., 2000), there are no known studies that have evaluated the reliability of the interference difference scores. While the reliability of these interference scores may be questioned, it is nevertheless important to note that many researchers using these interference scores in past studies have found evidence of abnormal susceptibility of interference in clinical samples relative to healthy controls, and thus it is unlikely that the use of these scores in the current study accounts for the null findings.

Timing of Psychosis Ratings

As previously described, BPRS ratings of psychosis in FE patients were not always assessed in proximity to the date of cognitive testing. Thus, it is possible that a patient's psychosis ratings may have changed somewhat between the date in which it

was assessed and the date of cognitive testing. While there is no known research examining the stability of psychotic ratings in the initial months of illness, an examination of the current data revealed that the number of days elapsed between BPRS ratings and cognitive testing did not significantly predict BPRS scores (as described in the methods section), indicating that longer time lags between symptom ratings and testing did not systematically influence the patients' psychosis ratings. Moreover, the current findings of no significant associations between interference effects and psychosis ratings in the FE schizophrenia sample remained stable even after controlling for the number of days elapsed between psychosis ratings and cognitive testing. Thus, it seems unlikely that the current lack of associations between interference effects and severity of psychosis in FE schizophrenia are attributable to delays in acquiring psychosis ratings. Although it still remains possible that an individual patient's symptom ratings may have changed between the time of rating and the time of cognitive testing, it is worth noting that cognitive dysfunction generally persists beyond the acute phases of illness with little evidence of dramatic changes in cognition with acute symptom resolution (for a review, see Lewandowski, Cohen, & Ongur, 2011).

Concluding Statements

Overall, results of the current study revealed normal PI and RI in FE schizophrenia patients. Although some associations between poorer executive functioning and greater interference emerged in FE patients in general, interference effects did not contribute significantly to eventual delayed recall. Given past findings of attenuated release from PI and heightened build-up of RI in chronic schizophrenia patients, the current findings suggest that verbal memory interference develops over time with further illness burden and/or ongoing antipsychotic medications. Future longitudinal studies examining interference effects in schizophrenia patients across the initial years of illness would help to further clarify the development of verbal memory interference in this disorder. It would be additionally interesting for future research to identify those factors (e.g., cognitive, clinical, neuropathological) that are associated with the development of these interference effects as they occur over time. Finally, future research should help to clarify the extent to which interference contributes to eventual

long-term memory in schizophrenia patients that are known to have attenuated release from PI and increased build-up of RI.

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Appendix A.

Participant Standardized Scores on Established Neuropsychological Measures

Variable	FES (*N* = 72)	Unmatched FEB (*N* = 64)	Unmatched HC (*N* = 105)	Matched FEB (*N* = 43)	Matched HC (*N* = 49)
K-BIT[a]					
Composite IQ	94.32 (10.23)	104.41 (9.84)	107.70 (9.63)	100.81 (8.81)	104.15 (9.30)
Vocabulary	91.72 (10.21)	100.65 (10.83)	105.11 (10.83)	96.37 (9.52)	99.88 (10.37)
Matrices	98.10 (11.65)	107.43 (10.37)	108.73 (9.92)	105.30 (10.20)	107.71 (11.05)
COWAT	-0.70 (0.93)	-0.52 (0.81)	-0.12 (0.96)	-0.57 (0.87)	-0.08 (1.01)
LNS[b]	7.49 (2.54)	9.81 (2.62)	11.06 (2.63)	9.19 (2.45)	10.43 (2.59)
CVLT-II					
Trial 1	-0.95 (0.87)	-0.36 (1.01)	0.01 (1.23)	-0.55 (0.95)	-0.07 (1.25)
Trial 5	-1.13 (1.32)	-0.53 (0.99)	0.32 (0.90)	-0.74 (1.05)	0.32 (0.94)
Trials 1-5[c]	41.12 (10.80)	49.62 (11.29)	56.78 (10.08)	47.16 (11.53)	56.59 (10.63)
List B	-0.95 (0.84)	-0.63 (0.89)	-0.05 (1.06)	-0.71 (0.90)	-0.15 (1.17)
SDFR	-0.92 (1.18)	-0.33 (1.12)	0.44 (0.94)	-0.58 (1.15)	0.47 (0.86)
SDCR	-1.04 (1.23)	-0.50 (1.17)	0.23 (1.01)	-0.78 (1.21)	0.19 (0.97)
LDFR	-1.13 (1.22)	-0.44 (1.14)	0.26 (1.05)	-0.63 (1.26)	0.32 (1.04)
LDCR	-1.11 (1.20)	-0.57 (1.15)	0.17 (0.98)	-0.84 (1.24)	0.19 (0.97)
Semantic Clustering	-0.54 (0.75)	-0.06 (1.05)	0.62 (1.46)	-0.06 (1.05)	0.56 (1.35)
Serial Clustering	0.36 (1.20)	0.19 (1.10)	0.01 (1.22)	0.04 (0.97)	-0.05 (1.33)
Primacy Recall	0.15 (1.37)	-0.19 (0.99)	-0.31 (0.82)	-0.16 (1.11)	-0.42 (0.68)
Middle Recall	-0.90 (1.53)	-0.15 (1.20)	-0.01 (1.04)	-0.19 (1.31)	0.08 (1.06)
Recency Recall	0.48 (1.43)	0.07 (1.13)	0.07 (0.78)	0.11 (1.16)	0.09 (0.86)
Learning Slope	-0.42 (1.09)	-0.33 (0.82)	0.20 (1.16)	-0.38 (0.81)	0.30 (1.19)
Recall Consistency	-0.40 (1.00)	-0.07 (1.17)	0.67 (0.76)	-0.23 (1.18)	0.62 (0.78)

Repetitions	0.26 (1.27)	0.61 (1.40)	0.47 (1.41)	0.56 (1.40)	0.68 (1.44)
Intrusions	0.46 (1.23)	0.56 (1.24)	0.06 (0.99)	0.83 (1.38)	0.06 (0.95)
Recognition	-0.73 (1.27)	-0.28 (1.19)	0.40 (0.90	-0.58 (1.23)	0.49 (0.74)

Note. Test performance is presented as mean standardized *z*-scores (*SD)* correcting for age (and education for the COWAT), unless otherwise specified. Normative data on United States populations were obtained from the original test publication manuals, with the exception of the COWAT in which Canadian normative data were available (Tombaugh, 1999). FES = first episode schizophrenia; FEB = first episode bipolar; HC = healthy controls; LNS = Letter-Number Sequencing; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test-II; SDFR = Short Delay Free Recall; SDCR = Short Delay Cued Recall; LDFR = Long Delay Free Recall; LDCR = Long Delay Cued Recall.

[a] Data represent mean Standard IQ scores (*SD)*.

[b] Data represent mean Scaled scores (*SD*).

[c] Data represent mean *T*-scores (*SD)*.

Appendix B.

Correlations of Background Variables and Interference Scores in FE Patients

	Build-up of PI	*p*-value	Release from PI	*p*-value	Build-up of RI	*p*-value
FE Schizophrenia (*N* = 72)						
PANSS						
Positive symptoms	0.14	.229	-0.09	.461	0.06	.599
Negative symptoms	-0.02	.841	0.09	.475	-0.08	.521
Disorganization symptoms	0.03	.833	-0.16	.184	-0.10	.393
Total score	0.03	.832	-0.10	.430	-0.06	.609
Matched FE Bipolar (*N* = 43)						
YMRS[a]	-0.13	.443	-0.07	.690	-0.19	.251
Lithium (0=no; 1=yes)	0.14	.379	-0.09	.564	-0.00	.996
Lithium Dose	0.20	.194	-0.14	.371	0.04	.803
Divalproex (0=no; 1=yes)	0.00	.999	0.05	.768	0.19	.205
Divalproex Dose	-0.03	.859	0.16	.318	0.14	.367
Combine FE Samples (*N* = 115)						
Age	0.03	.726	0.09	.360	-0.07	.429
Gender (0=female; 1=male)	0.02	.877	0.06	.551	-0.02	.862
Premorbid IQ (NAART)	0.13	.160	-0.09	.333	-0.06	.523
Age of Illness Onset	0.03	.725	0.03	.742	-0.10	.319
Time Since Initial Symptoms	0.09	.384	0.06	.551	0.04	.692
BPRS Total Score	-0.08	.382	-0.02	.843	-0.08	.387
Depression Rating[b]	-0.02	.810	0.03	.740	0.05	.565
Time on Psychotropics[c]	0.12	.195	-0.03	.755	0.06	.555
CPZ Equivalents[c]	0.06	.537	0.07	.470	0.05	.594
Alcohol (0=no; 1=yes)[d]	0.04	.689	0.12	.211	-0.14	.155
Marijuana (0=no; 1=yes)[e]	0.02	.851	0.17	.063	0.01	.960

Note: FE = first episode; PANSS = Positive and Negative Syndrome Scale; NAART = North American Adult Reading Test; BPRS = Brief Psychiatric Rating Scale; CPZ = chlorpromazine.

[a] Inverse transformed.

[b] Rating obtained from BPRS Item 9 (depressive mood).

[c] Square root transformed.

[d] Refers to lifetime DSM-IV alcohol abuse.

[e] Refers to current DSM-IV marijuana abuse.

Appendix C.

Correlations of Background Variables and Delayed Verbal Recall in FE Patients

	Correlation Coefficient	*p*-value
FE Schizophrenia (*N* = 72)		
PANSS		
Positive symptoms	-0.02	.880
Negative symptoms	-0.05	.699
Disorganization symptoms	-0.02	.847
Total score	-0.07	.590
Matched FE Bipolar (*N* = 43)		
YMRS[a]	0.12	.486
Lithium (0=no; 1=yes)	-0.11	.466
Lithium Dose	-0.17	.278
Divalproex (0=no; 1=yes)	0.10	.516
Divalproex Dose	0.12	.444
Combined FE Samples (*N* = 115)		
Age	-0.08	.399
Gender (0=female; 1=male)	-0.20	.028
Premorbid IQ (NAART)	0.18	.057
Age of Illness Onset	-0.05	.608
Time Since Initial Symptoms	-0.01	.900
BPRS Total score	**-0.25**	**.008**
Depression Rating[b]	-0.06	.523
Time on Psychotropics[c]	0.03	.785
CPZ Equivalents[c]	-0.16	.096
Alcohol (0=no; 1=yes)[d]	-0.21	.028
Marijuana (0=no; 1=yes)[e]	-0.14	.143

Note: BPRS Total score (bolded) was found to predict at least 5% of the variance in Long-Delay Free Recall on the California Verbal Learning Test-II. FE = first episode; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale; NAART = North American Adult Reading Test; BPRS = Brief Psychiatric Rating Scale; CPZ = chlorpromazine.

[a] Inverse transformed.

[b] Rating obtained from BPRS Item 9 (depressive mood).

[c] Square root transformed.

[d] Refers to lifetime DSM-IV alcohol abuse.

[e] Refers to current DSM-IV marijuana abuse.