

**MULTIPLE MEMORY SYSTEMS IN PEOPLE WITH
SCHIZOPHRENIA: POSSIBLE EFFECT OF ATYPICAL ANTI-
PSYCHOTIC MEDICATIONS**

by

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Abstract

Patients with schizophrenia are normally treated with one of several antipsychotic medications that differ from one another in the areas of the brain they affect including the dorsal striatum, a subcortical section of the forebrain, and the prefrontal cortex (PFC), located in the anterior part of the frontal lobes. Two different tests of implicit memory, the probabilistic classification learning (PCL) and the Iowa gambling task (IGT), have been shown to rely on the dorsal striatum and the PFC, respectively. Studies have previously shown that patients with schizophrenia treated with antipsychotics that affect the dorsal striatum (e.g., risperidone), have altered performance on the PCL, and those treated with antipsychotics that affect the PFC (e.g., clozapine), have altered performance on the IGT. We tested the hypothesis that patients with schizophrenia treated with olanzapine would have a poorer performance on the IGT, but not the PCL, when compared with controls. This study aimed to clarify conflicting results from prior experiments observing the effects of olanzapine on implicit memory in people with schizophrenia. We also hypothesized that performance of patients taking aripiprazole would be comparable to those taking risperidone, or an FGA; however, we were unable to recruit a sufficient amount of participants to test this hypothesis. Patients with schizophrenia, a mental disorder characterized by a breakdown in relation between thoughts, emotion, and behavior, treated with olanzapine were recruited through local psychiatric clinics or using a newspaper ad. Administration of the Brief Psychiatric Rating Scale (BPRS) and the Mini Mental State Examination (MMSE) preceded a brief questionnaire of demographic information. Participants were tested on the PCL and the

IGT using a personal computer. Results revealed poorer performance on both the MMSE and BPRS for patients when compared with controls. Patients taking olanzapine were impaired in learning the PCL but not the IGT when compared with controls. Results suggest that olanzapine acts on the PFC to augment IGT performance but further studies are needed.

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List of Abbreviations

5-HT	5-Hydroxy Tryptamine
ACC	Anterior Cingulate Cortex
AMPA	Amino-Methyl-Propanoic Acid
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
DA	Dopamine
DLPFC	Dorso-Lateral Prefrontal Cortex
DTNBP1	Dysbindin
EPS	Extra-Pyramidal Side Effects
FGA	First Generation Antipsychotic
FLI	Fos-Like Immunoreactivity
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GSR	Galvanic Skin Response
i.p.	Intraperitoneal Injection
IGT	Iowa Gambling Task
IPAP	International Psychopharmacology Algorithm Project
KA	Kainic Acid
LSD	Lysergic Acid Diethylamide
mGluR	Metabotropic Glutamate Receptor
mRNA	Messenger Ribonucleic Acid

MRS	Magnetic Resonance Spectroscopy
NDM	Non-Declarative Memory
NE	Norepinephrine
NMDA	N-Methyl D-Aspartate
NRG-1	Neuregulin-1
OFC	Orbital Frontal Cortex
PANSS	Positive And Negative Syndrome Scale
PCL	Probabilistic Classification Learning
PCP	Phencyclidine
PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
QLS	Quality of Life Scale
RCT	Randomized Controlled Trial
s.c.	Sub-Cutaneous
SGAs	Second Generation Antipsychotics
SN	Substantia Nigra
SNPs	Single Nucleotide Polymorphism
SRT	Serial Reaction Time
TGAs	Third Generation Antipsychotics
ToM	Theory of Mind
VMPFC	Ventro-Medial Prefrontal Cortex

WCST

Wisconsin Card Sorting Task

WPT

Weather Prediction Task

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Chapter 1

Introduction

1.1 Schizophrenia

Schizophrenia is a severe and debilitating mental illness that has a worldwide prevalence near 1%. The disorder is characterized by both positive and negative symptoms and identified as a deterioration of thought processes and deficient emotional responsiveness. Cognitive deficits may affect memory, learning, attention, reasoning, and decision making, to name a few. Positive symptoms include hallucinations, delusions, as well as disordered thoughts and speech. Negative symptoms involve blunted affect, alogia (poverty of speech), anhedonia (inability to experience pleasure), asociality (lack of interest in social engagement), and avolition (lack of motivation) (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012). The past two decades have brought about an influx of research into the etiology of the disorder as well as treatment options for the symptomatology that defines it. Understanding of schizophrenia is still evolving, and research is advancing what we know about neurobiology both through the uniqueness of neurochemical changes and behavioural alterations that have become hallmarks of the disorder. Investigating these differences provides scientists with a better understanding of the complexity of the disorder along with the brain itself (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012).

Antipsychotic medications remain the frontline of treatment for people with schizophrenia. First generation antipsychotic medications (FGA) or typical antipsychotics were discovered to block dopamine (DA) D2-like receptors in the brain, and this led to the dopamine (DA) hypothesis of schizophrenia suggesting that hyperactivity of the mesolimbic DA system underlies schizophrenia (Miyake, 2012; Purdon, 2003; Wan, 1995). Dopaminergic neurons sprouting axons from the Ventral Tegmental Area (VTA) Substantia Nigra (SN) and hypothalamus give rise to four major anatomically defined pathways in the brain: they are the mesocortical (with projections from the VTA to the frontal cortex), mesolimbic (projections from the VTA to the limbic system via the nucleus accumbens), nigro-striatal (substantia nigra to the striatum), and tuberoinfundibular (hypothalamus to the pituitary gland) pathways.

FGAs started with chlorpromazine in 1952 followed by a number of others including haloperidol and loxapine (Marder, 2004; Miyake, 2012). As the symptomatology of schizophrenia involves both positive and negative symptoms there is a drawback in FGA treatment in that it does not remedy negative symptoms despite being effective in reducing positive symptoms. This can leave patients suffering from rather enervating extra pyramidal side effects (EPS) that result in several movement disorders such as tardive dyskinesia, and other side effects such as hyperprolactinemia (abnormally high levels of prolactin in the blood), particularly with long-term exposure to FGAs (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012).

The emergence of clozapine in 1989 represented the second generation, or atypical, antipsychotics (SGAs) in that it showed superiority over the previous FGAs in treatment-resistant schizophrenia due to the lack of EPS, although it comes with the added risk of agranulocytosis, a blood disorder that can be fatal (Miyake et al., 2012). Over the following decade numerous SGAs, including risperidone and olanzapine, were introduced representing success over FGAs in terms of lowered EPS and superiority when compared with clozapine because they did not cause agranulocytosis (Kukshal, 2012; Miyake, 2012). However, many SGAs result in increased metabolic side effects such as glucose dysregulation, weight gain, and dyslipidemia (abnormal level of lipids in the blood), when compared with FGAs, yet may be more beneficial in terms of quality of life, cognition (involving effects on memory, attention, learning, language, and decision making), and preventing relapse. Although it is unclear that SGAs are conclusively superior, they remain a more widely used treatment over FGAs in treating schizophrenia (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012).

The advent of new research into the biological basis for efficacious pharmacotherapy has ushered in a “revised DA hypothesis of schizophrenia” as well as a “serotonin-DA hypothesis” (Miyake et al., 2012). The former concerns the divergent neuro-correlates of both positive and negative symptoms within schizophrenia, wherein positive symptoms arise from hyperactivity of the mesolimbic DA pathway and negative symptoms result from a hypoactive mesocortical DA pathway in the frontal cortex. This would explain the lack of efficacy in antipsychotic DA antagonists reducing negative

symptoms (Westerink et al., 2002). Unlike with FGAs whose affinity for antagonism of the D2 receptor defines this class of antipsychotics, SGAs share less in common in terms of a distinct pharmacological profile. One unifying characteristic among most SGAs is powerful antagonism of 5-hydroxy-tryptamine (5-HT) 2a receptors along with weaker blockade of the D2 receptor (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012). The objective is increased antipsychotic function and reduced EPS; however, an inadequacy in this theory is that those drugs that have weak D2 antagonism are given at significantly higher doses compared with drugs that have a more powerful antagonism at this receptor regardless of affinity for the 5-HT2a receptor (Kukshal, 2012; Miyake, 2012).

Aripiprazole, a novel antipsychotic approved in 2002, is the first in a new line of medications referred to as third generation antipsychotics (TGAs) due to their unique pharmacological action. It is argued that TGAs can display various combinations of antagonism, or partial agonism, at both 5-HT1a and D2 receptors (Kukshal, 2012; Miyake, 2012; Narayanaswamy, 2012).

Both FGA and SGA medications differentially affect disparate brain areas including those regions that process memory. Both declarative memory, which involves facts and knowledge that can be recalled consciously, and non-declarative memory (NDM), which involves the non-conscious acquisition of skills, can be dissociated anatomically. Declarative memory functions are impaired following damage to medial temporal or diencephalic structures, and NDM, and its subdivisions, rely on numerous brain structures including the striatum and ventro-medial prefrontal cortex (VMPFC).

Two tasks widely used in the literature to assess NDM are the Iowa Gambling Task (IGT) and the Weather Prediction Task (WPT) which is a probabilistic classification learning (PCL) task. Prior research has shown that patients taking FGAs generally show impaired performance on the PCL and those taking SGAs show impaired performance on the IGT, a double dissociation (Beninger et al. 2003; Wasserman et al., 2012).

The goal of this study was to assess the impact of specific SGA medications on NDM in people with schizophrenia using the IGT and PCL. I tested the hypothesis that those taking olanzapine will have a significantly poorer performance on the IGT, but not the PCL, when compared with controls. Demographic information including gender, age, and education, along with performance on the Mini Mental State Exam (MMSE) and the Brief Psychiatric Rating Scale (BPRS) was also collected.

Neurobiological theories of schizophrenia, pharmacological actions of antipsychotics, and investigations into multiple memory systems are presented in the following literature review.

Chapter 2

Literature Review

2.1 Etiology

Schizophrenia as a disorder was first classified in the early 20th century by psychiatrist Kurt Schneider. Since then numerous revisions have taken place in an attempt to distinguish schizophrenia from other psychiatric conditions. The causes for the disorder are varied and complex and include contributions from genetic, environmental, developmental, and substance misuse factors; up until the 21st century the established view was that schizophrenia had an unknown etiology (Opler, Perrin, Kleinhaus, & Malaspina, 2008). There is an incomplete knowledge of the molecular mechanisms of schizophrenia pathophysiology. Epidemiological studies have revealed that schizophrenia is impacted by environmental conditions such as urban birth or residence, famines, migrant status and seasonal effects. Cerebral hypoxia, prenatal infections, advanced paternal age, and other critical pregnancy complications represent some of the environmental risk factors that may occur before birth (Gejman, Sanders, & Duan, 2010). Heritability estimates vary from 71% to 85%, where concordance rates among dizygotic twins range from 4% to 17% and vary 44% to 79% in monozygotic twins supporting the supposition of a genetic contribution to the disorder (Opler et al., 2008).

Numerous studies have found positive results between schizophrenia and single nucleotide polymorphisms (SNPs) and haplotypes of the neuregulin (*NRG1*) gene located

on chromosome 8p (Opler et al., 2008). Expression of *NRG1* is associated with many biological functions including neuronal migration and specification, neuron-glia signaling, glial and synapse development, myelination, as well as regulation of N-methyl-D-aspartate (NMDA), γ -aminobutyric acid-A (GABA-A) and nicotinic receptors. Dysbindin, or dystrobrevin-binding protein 1 (*DTNBP1*), located on chromosome 6p22.3 is under expressed in people with schizophrenia leading some to suspect that this may alter synaptic connectivity and glutamate signaling with an effect most pronounced on prefrontal brain function (Opler et al., 2008). Research continues to elucidate the complex mixture of both environmental and genetic factors that gives rise to schizophrenia and its subdivisions.

2.2 Symptomatology Course and Outcome

The neurodevelopmental hypothesis of schizophrenia characterizes the environmental and biological risk factors that affect development of the brain; however, there is not an adequate description of the mechanisms mediating risk factors that lead to the phenotype of psychosis. The prodromal phase of the illness is linked with cognitive impairment, wherein the severity is associated with transformation into psychosis. Present in both early and adult onset psychosis, cognitive impairment is thought to be one of the core features of schizophrenia and includes deficiencies in attention, memory, and executive functions (Remberk, Namyslowska, & Rybakowski, 2012).

Positive symptoms, including hallucinations and delusions, which are well treated with antipsychotics, and negative symptoms, including blunted affect, lack of motivation,

and poverty of speech, remain less well treated despite advances in SGAs over FGAs in reducing EPS liability, with outcomes such as parkinsonian syndrome due to widespread D2 receptor antagonism (specifically through projections from the substantia nigra to the corpus striatum) (Honey et al., 1999). The negative symptomatology of schizophrenia is also characterized by disorganization symptoms, such as disruptions in syntax and behavior along with severe mood symptoms that may include manic or major depressive episodes (Gejman et al., 2010).

Abnormalities in frontal lobe functioning have long been considered to be fundamental to the pathophysiology of schizophrenia. Structural and functional neuroimaging of both the orbital frontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) have shown abnormalities (e.g. significant reductions in volume and decreases in activation) in persons with schizophrenia, providing a neuroscientific basis for impairments in complex decision making processes, particularly in social or emotional decision making (Shurman, Horan, & Nuechterlein, 2005). The International Psychopharmacology Algorithm Project (IPAP) recommends eight situations be reviewed when doing an initial clinical assessment with someone presenting with possible schizophrenia. This assessment informs decisions toward hospitalization, outpatient clinics, prognosis of disease, and treatment options. The situations include the risk of suicide, incidence of agitation or severe aggressiveness, presence of catatonia, or neuroleptic malignant syndrome, prior history of non-compliance and side-effects,

comorbidity with affective (depressive or manic) symptoms, and substance abuse either in the case of a first episode or the prodromal phase (Gadelha, Noto, & De Jesus, 2012).

There are disagreements in the literature about gender-based cognitive impairments in people with schizophrenia with some studies showing greater impairments for men and vice versa, with other studies showing no significant sex differences. This variation in results is affected by such factors as sampling bias, insufficient sample size, disparities in illness severity, and lack of healthy female controls for proper comparisons during statistical analyses (Han et al., 2012).

Considerable research has focused on the pathophysiology of schizophrenia with efforts to describe and attenuate deficits. The most pronounced neuropsychological deficits revealing impairments in executive functioning pertain to tests of response inhibition (impulse control), set shifting (adapting to new rules), and selective attention along with deficits in language abilities, processing speed, working memory, verbal and visual memory (delineating the contribution of multiple brain areas) (Narayanaswamy et al., 2012). Numerous studies have looked at the course and outcome of the illness, and several factors have been identified as predictors. Factors yielding a more positive outcome include female gender, married status, early treatment, acute onset of illness, rural background, cohesive family, absence of negative symptoms, predominance of elaborate positive symptoms, short duration of first episode, scarcity of episodes concerning similar illness in the past, as well as having a good premorbid personality and adjustment profile (Rangaswamy & Greeshma, 2012). Factors producing a more negative

outcome in patients include male gender, unmarried status, younger age of illness onset, delayed or irregular treatment, subtle or gradual onset of illness, lack of support socially, increased number of negative symptoms, family history of schizophrenia or major psychoses, enlarged ventricles in the brain along with other neurological hallmarks, a history of alcohol dependence or substance abuse in general, as well as a poor record of occupational and social functioning prior to illness onset. Although these factors have been predictors, few studies have been able to tease out confounding variables involving cultural bias, sample selection, definition of outcome, and working diagnostic criteria in terms of discerning a positive course and outcome (Rangaswamy & Greeshma, 2012).

2.3 Biological Theories of Schizophrenia

2.3.1 Dopamine Hypothesis

In psychiatry, the DA hypothesis of schizophrenia is one of the most enduring and prominent etiological theories and is still widely cited (Baumeister, 2002; Howes, 2009; Kendler, 2011). The revised hypothesis takes into account a subcortical/cortical discontinuity wherein subcortical mesolimbic DA projections are suspected to be hyperactive leading to positive symptoms and overstimulation of D2-like receptors. Conversely mesocortical projections to the prefrontal cortex may be hypoactive leading to under-stimulation of D1-like receptors associated with cognitive impairment and negative symptoms (Walter, Kammerer, Frasch, Spitzer, & Abler, 2009).

The first significant realizations in the development of the hypothesis came in the early 1960's following identification of monoamine neurotransmitters as mediators between nerve cells with histofluorescence allowing for pathways to be traced. Despite its meager beginnings in research, DA has gone from being viewed simply as a precursor molecule with diminutive operational significance to the primary malfunctioning neurotransmitter in schizophrenia, although that title remains under question (Howes et al., 2009). When Carlsson and Lindqvist were studying the actions of neuroleptic drugs (already effective in the treatment of schizophrenia) on DA turnover in the rodent brain, the significance of abnormal DA functioning became central to understanding schizophrenia (Howes, 2009; Kendler, 2011). Regarding the nigrostriatal, retinal, and tuberoinfundibular pathways as being unlikely to result in the symptomatology of psychosis seen in schizophrenia, progress in the theory was made in presuming the mesolimbic DA system as being likely to impact the perceptual, emotional, and cognitive functions altered in the disorder. It was also noted that high doses of amphetamines could induce schizophrenia-like psychosis and paranoia in otherwise non-psychotic people (Howes, 2009; Kendler, 2011). Further support came from observations that reserpine, a drug effective in the treatment of psychosis, was found to stop the vesicular reuptake of monoamines, including DA, leading to a decline in DA release (Baumeister, 2002; Howes, 2009).

Research in the 1970's gave way to further insights suggesting numerous DA hypotheses of the etiology of schizophrenia, including faulty feedback loops, underactive

antagonistic neurochemical systems, excessive release of DA at synapses, and hypersensitive DA receptors (Kendler et al., 2011). In 1979 the two DA receptor subtypes D1 and D2 were isolated, and this along with the previous discovery of autoreceptors helped shape a working model of how the DA hypothesis may be empirically verified. Identification of genes coding for DA receptors occurred in the 1980's through to the early 1990's adding detail to how DA dysfunction may give rise to the symptomatology of schizophrenia (Kendler et al., 2011). There are five G-protein coupled DA receptors divided into two families. The D1-like receptors (including D1 and D5) activate the enzyme adenylyl cyclase resulting in increases of intracellular cyclic adenosine monophosphate (cAMP), whereas the D2-like receptors (including D2, D3, and D4) inhibit adenylyl cyclase and thus cAMP.

By the early 1990's the hypothesis was advanced with the inclusion of regional specificity to explain findings concerning metabolites which were not unanimously elevated in the cerebrospinal fluid (CSF) or serum of patients with schizophrenia (Howes et al., 2009). Results from post-mortem analyses and imaging data, in addition to experiments with animals into cortical/subcortical interplay also had to be included (Westerink et al., 2002). Furthermore the discovery that clozapine was more efficacious than other antipsychotic medications for patients with refractory (treatment resistant) schizophrenia, despite having low affinity for D2 receptors, called into question the simplicity of the original hypothesis. Moreover early positron emission tomography (PET) studies of D2/3 receptors in drug-naïve patients showed inconsistent results, while

post-mortem studies of the D2 receptor in patients with schizophrenia could not eliminate the confounds of prior treatment with antipsychotics (Howes et al., 2009).

Only a few investigations into the possible functioning of the mesolimbic DA system using functional magnetic resonance imaging (fMRI) on patients with schizophrenia have occurred with tasks exploring the reward system. In anticipation of a potential financial reward, in both unmedicated patients and those treated with FGAs, hypoactivation of the ventral striatum occurred along with an inverse relationship between said activation and negative symptoms. However, normal reward-related activation of regions of the mesolimbic system innervated by DA was observed in patients treated with SGAs (Walter et al., 2009). The greatest evidence for regional specificity has come from PET studies revealing decreased cerebral blood flow in the frontal cortex which has been directly correlated with low CSF DA metabolite levels. Animal studies have supported this relationship wherein lesions to the PFC result in increased levels of DA, and its metabolites, as well as increased D2 receptor density in the striatum, whereas DA agonists directed at prefrontal areas lead to reduced DA metabolite levels in the striatum (Howes et al., 2009).

A drawback to the DA hypothesis of schizophrenia comes from being able to validate the empirical evidence from animal studies starting with whether higher density of D2 receptors in the brains of people with schizophrenia is due to the disorder or drug treatment. Issues concern the dearth of drug-naïve patients post-mortem as well as poorly matched studies on gender reviewing D2 receptor density, leading some to assert that

abnormalities in D2 receptor density are more so the result of medication (Kendler et al., 2011). Another shortfall in the DA hypothesis of schizophrenia involves its tendency for explaining a highly complex disorder too simply, as it is not obvious that DA transmission is the principal deficit in schizophrenia (Walter et al., 2009). Environmental and genetic risk factors influence presynaptic hyperdopaminergic striatal functioning leading to abnormal postsynaptic binding of D2 receptors. This can result in psychotic-like symptoms wherein antipsychotics that reduce these symptoms by binding downstream to postsynaptic receptors account for only part of the model explaining schizophrenia, further delineating an inadequacy in the DA hypothesis (Howes et al., 2009). The DA hypothesis of schizophrenia is no different than the DA hypothesis of psychosis as DA receptor antagonists usually do little for cognitive or negative symptoms, representing another shortcoming of the DA hypothesis. Finally, the role of glutamate, GABA, serotonin, and other neurotransmitters needs to be accounted for in attempting to provide a more holistic explanation of this disorder.

2.3.2 Glutamate Hypothesis

Despite longstanding robust interest in DA as the primary neurotransmitter behind the symptomatology of schizophrenia, other neurotransmitters have been incorporated to provide a more comprehensive explanation, especially with regard to negative symptoms. Glutamate is the primary excitatory neurotransmitter in the mammalian brain and the hypothesis posits that a deficiency in glutamate neurotransmission underlies a significant part of the symptomatology in schizophrenia (Akhondzadeh, 1998; Moghaddam, 2012).

The major receptor types that glutamate binds to are the metabotropic glutamate receptor (mGluR), along with three ionotropic receptors: kainic acid (KA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and NMDA, with the latter being the most important to the hypothesis as well as a receptor central to the study of learning and memory (Gordon, 2010; Ishimaru, 1997).

The glutamate hypothesis has its origins in the 1980's when it was noticed that there was a significant reduction in glutamate when looking at the CSF of patients with schizophrenia compared with controls, however this result failed to be replicated in several studies afterwards (Ishimaru, 1997; Moghaddam, 2012). Suspicions about the role of glutamate in schizophrenia had appeared earlier, namely with the psychosis-like effects of phencyclidine (PCP) and ketamine, but there was not a direct connection to glutamate due to the broad range of interface with other transmitters including DA, norepinephrine (NE), 5HT, and acetylcholine (Ishimaru, 1997; Moghaddam, 2012). Unlike amphetamines which mostly mimic the positive symptoms of schizophrenia, PCP mimics both the positive and negative symptoms. Both PCP and ketamine are noncompetitive antagonists at the NMDA receptor, and enter the ion channel to block calcium ions from entering the cytoplasm (Ishimaru, 1997; Moghaddam, 2012).

Numerous studies using radiolabelled receptor assays in post-mortem tissue have tracked region-specific changes, with increased binding of KA in the prefrontal cortex (PFC) and decreased binding in the hippocampus, however, attempted replication of these results have not been consistent. Glutamate interacts extensively with DA in DA-

rich areas signifying a complex and important relationship between the two transmitters (Akhondzadeh, 1998; Ishimaru, 1997). The psychosis-inducing action of drugs like PCP may rely on DA modulation in giving rise to positive symptoms, and conversely, this increase in DA activity may indirectly result in glutamatergic hypoactivity in cortical areas. Decreases in DA turnover in the striatum, while increases in other regions (both mesocortical and mesolimbic terminal areas) have followed systemic administration of PCP in rats. It is suspected that PCP may disinhibit DA neurons in the PFC as NMDA receptors in this region mediate a tonic inhibition that regulates DA neurotransmission (Ishimaru, 1997; Moghaddam, 2012).

The possible influence of antipsychotic drugs on glutamatergic neurotransmission is an area continuously under study. FGAs predominantly do not have an effect on the glutamatergic system, however, they have been shown to upregulate NMDA receptors and reverse impaired glutamate release *in vivo*. SGAs, such as clozapine, have been shown to antagonize the behavioural effects and neurotoxicity provoked by NMDA receptor antagonists (Ishimaru, 1997; Moghaddam, 2012). Abnormalities in fast-spiking cortical GABA interneurons have also been found, wherein reduced NMDA receptor signaling could cause the interneurons to decrease their own activity in an attempt to restore balance between excitation and inhibition, further adding to the complexity of the neurochemical underpinnings of schizophrenia. Specifically, in the cortical interneuron population, these deficiencies in NMDA receptor activity could lead to the GABA

deficits seen in schizophrenia (Gordon et al., 2010). This interaction represents the importance of GABA in the etiology of schizophrenia symptomatology.

2.3.3 GABA Hypothesis

GABA was initially discovered in fungi, bacteria, and plants, and later found in the mammalian brain in 1949. It is the primary inhibitory neurotransmitter in the brain and is synthesized via decarboxylation from its precursor L-glutamate (Tayoshi et al., 2010). There are three GABA receptor types, two of which are ionotropic: GABA_A and GABA_C, whereas GABA_B is metabotropic. The PFC is implicated in the pathophysiology of schizophrenia, and this area displays tonic inhibition of striatal DA projections, presumably mediated by GABA interneurons within the PFC (Tayoshi et al., 2010). Experiments with both FGAs and SGAs indicate that they affect levels of extracellular GABA both by reducing GABA in the PFC and increasing concentrations in the pallidum, although there is disagreement in the literature about their effects on the striatum (Wassef, Baker, & Kochan, 2003).

In rat studies with doses much higher than humans would receive, olanzapine (2.5–10.0 mg/kg) and clozapine (5.0–20.0 mg/kg) resulted in increased levels of a strong GABA_A receptor modulator, allopregnanolone, in the cerebral cortex indicating one potential mechanism underlying the antipsychotic effect of both drugs on the GABA system. However, neither risperidone nor haloperidol had an effect on allopregnanolone levels implying that olanzapine and clozapine are atypical with regard to their effect on GABA receptors (Wassef et al., 2003). Furthermore, in a study looking at the effect of

SGAs on GABA concentrations with magnetic resonance spectroscopy (MRS), Goto et al. (2005) found no significant differences between pre-treatment and six months post treatment for first-episode or early stage patients with schizophrenia when compared with controls.

The GABA hypothesis of schizophrenia was initially based on the assumption that the primary mechanism of inhibition for the nigro-striatal dopaminergic system, through a negative feedback loop, is GABA-containing neurons originating in the caudate nucleus of the striatum (DeliniStula & BerdahTordjman, 1995). The hypothesis was supported when it was observed that both psychotic-like symptoms and hyperactivity of dopaminergic neurons followed blockade of GABA neurons in cats (DeliniStula & BerdahTordjman, 1995). However, vanKammen et al. (1998) suggested that impaired GABA transmission is not a large-scale phenomenon in the brain, due to a significant relationship between sulcal widening in the PFC alone and plasma GABA in patients with schizophrenia. The effect of GABA on DA has been widely studied and several key findings highlight its influence in the neurochemical model of schizophrenia etiology. Low concentrations of GABAergic compounds enable release of DA when working on resting dopaminergic cells. However, when there are high concentrations of GABA in the presence of active dopaminergic cells, GABA reduces the release of DA indicating a modulatory role of GABA on DA in different brain areas (Wassef et al., 2003).

Using brain samples from patients who had schizophrenia it was found that markers of GABAergic neurons were decreased while postsynaptic receptor complexes

were increased (Petryshen et al., 2005). Moreover, there is evidence that *NRG1* and *DTNBPI*, highlighted as candidate risk genes for schizophrenia, interact with the GABA_A receptor (Petryshen et al., 2005). In clinical trials with GABAergic agents there have been conflicting reports. Some studies have suggested that GABAergic agents were ineffective in the treatment of schizophrenia, with other studies observing the appearance of stark schizophrenia symptomatology during withdrawal states from GABAergic drugs (Wassef et al., 1999).

There have been several post-mortem human brain studies; however, many, especially earlier studies, are confounded by factors such as the retroactive process of collecting information, shortage of details about specific symptomatology, time lapses preceding sample assays, and the influence of long-term intake of antipsychotic medications on the GABA system (Wassef et al., 2003). Evidence of a dysfunction of inhibitory GABAergic interneurons has been provided by several post-mortem studies (Benes et al., 2009). GABA interneurons modulate the output of projections from limbic and cortical pyramidal cells to other brain structures via inhibitory effects. Decreases in calcium binding protein in calcium binding immunoreactive neurons in the anterior cingulate cortex (ACC) were found in patients with schizophrenia when compared with controls (Wassef et al., 2003). There have also been findings of reduced GABA uptake sites in the temporal lobe of patients with schizophrenia in autopsy studies (vanKammen et al., 1998). Binding studies with nipecotic acid, which is a ligand marked for GABA uptake sites, has revealed decreased GABA uptake bilaterally in the hippocampus,

amygdala, and left temporal cortex of patients with schizophrenia (Wassef et al., 2003). A related study found a correlation between increased DA in the amygdala and decreases in GABA in the left hemisphere; however, a follow-up study failed replication of these results (Wassef et al., 2003). There have also been notable reductions in chandelier cells, a group of GABA interneurons in the DLPFC that exert a modulatory inhibition over excitatory pyramidal cells, in patients with schizophrenia when compared with controls (Volk, 2005; Wassef, 2003).

It is suspected that a reorganization, and perhaps amplification, of cognitive, sensory, and memory fields, due to decreased cortical GABAergic action could be responsible for the disorganized thinking seen in schizophrenia. Furthermore, when bicuculline, a GABA_A receptor antagonist, was injected into the PFC of macaque monkeys while they performed a delayed-response task, the researchers observed errors in working memory presumably as a result of GABA disruption (Wassef et al., 2003). GABA neurons seem to be an essential part of neural systems that facilitate working memory processes and coordinated pyramidal neuron activity (Volk et al., 2005). It has previously been demonstrated that working memory performance is affected by GABA-modulating drugs and that these drugs result in activation changes in the ACC of patients with schizophrenia; however, Tayoshi et al. (2010) found no significant changes to GABA concentrations in the ACC of patients with schizophrenia when compared with controls. The hypothesized cause of the augmented GABA_A receptor binding in the

cingulate cortex, PFC, and hippocampal formation is the diminished density of cortical interneurons in both the cingulate and prefrontal cortices (vanKammen et al., 1998).

Individually or in combination DA, serotonin, glutamate, or GABA could disrupt prefrontal circuitry necessary for working memory, underlying cortical dysfunction in schizophrenia, however, changes to other neurotransmitters, for example adrenergic and cholinergic neurotransmission, further delineates the complexity (Goldman-Rakic & Selemon, 1997). The blunted affect and general emotional dysfunction seen in schizophrenia may be due to disturbances in limbic GABA neuronal activity, and in studies looking at the topographical organization of the GABA pathways in the basal ganglia and limbic system there is evidence suggesting GABA neurons not only constitute a negative feedback but a feed-forward inhibition with nigro-striatal connections as well (Delini-Stula, 1995; Wassef, 2003). The effect of GABA on schizophrenia symptomatology and changes following antipsychotic treatment continue to be investigated. Through direct effects within regions of interest, e.g., the PFC, and its working in concert with other neurotransmitters, GABA continues to be prevalent in the neurochemical description of schizophrenia.

2.3.4 Serotonin Hypothesis

5-HT was first discovered as a vasoconstrictive substance that was later isolated and named serotonin in the late 1940's. Through the 1950's and 1960's serotonin's role emerged through pharmacologic assays, implicating it in specific brain structures, along with emerging details of its synthesis and metabolism, followed by mapping of serotonin

pathways in the brain (Baumeister & Hawkins, 2004). The serotonin hypothesis arose from toxicological theories of mental illness which contained hypotheses holding that symptomatology, like that seen in schizophrenia, may be caused by unusual metabolic processes that follow catecholamine biosynthesis. This later gave rise to insights into other disorders including the 5-HT hypothesis of depression. It was presumed, with the advent of research into lysergic acid diethylamide (LSD), that there was antagonism of 5-HT throughout the brain, wherein it was suggested that a deficiency in serotonin may underlie schizophrenia (Baumeister & Hawkins, 2004). Several assays of LSD revealed its action is more as an agonist of 5-HT than the reverse, and contradictory theories, regarding the original hypothesis, started to take hold suggesting that schizophrenia may be a result of overactive 5-HT (Baumeister, 2004; Geyer, 2008).

Taking a back seat to the prominence of the DA hypothesis it was not until the arrival of SGA medications that there was a significantly revived interest in the role of 5-HT in schizophrenia (Baumeister & Hawkins, 2004). In the literature looking at 5-HT and antipsychotic medication there are 15 polymorphisms of interests in eight receptor genes (5-HT₁, 2a, 2c, 3a, 3b, 5, 6, and 7); however, all studies were population based case control studies with more than two-thirds of them producing negative results. Ethnicity represented a potential confounding factor and only a few studies examined more than one gene variant at a time (Muller, De Luca, & Kennedy, 2003).

One such study looking at the effect of a gene variant of the 5-HT_{1a} receptor (C-1019) on responsivity to either risperidone or haloperidol, after four weeks of treatment,

found that the variant influenced the response to risperidone via a reduction in negative symptoms for those with the C allele versus those with the GG genotype; this difference was only present when patients were stratified according to 5-HT1a receptor genotype (Mossner et al., 2008). Uçok, Alpsan, Cakir, & Saruhan-Direskeneli (2007) studied the polymorphism of the 5-HT2a gene at codon 102 using sequence-specific polymerase chain reaction (PCR) on patients with schizophrenia who performed the Wisconsin card sorting task (WCST), used to measure executive functioning. However, all patients were in the remission phase of the illness and were taking both SGA and FGA medications. Those who had the TC genotype had significantly fewer incorrect responses when compared with those who were type CC or TT (Uçok et al., 2007).

In drug-naïve patients with schizophrenia, as well as at-risk subjects, there are significant reductions in the density of the 5-HT2a receptor in the PFC suggesting that abnormalities in serotonergic functioning may predate the onset of schizophrenia (Geyer et al., 2008). In both patient and animal models, antagonism of the 5HT2a receptor has been shown to be a therapeutic facet of SGA medications. Psilocybin, a psychedelic drug, has an affinity for several 5-HT receptors, including 5-HT2a, and acts as a partial agonist mimicking the activities of serotonin. PET studies with healthy human volunteers treated with psilocybin have shown similar metabolic changes indicative of hyperfrontality seen in acute schizophrenia (Geyer et al., 2008). Many post-mortem studies reveal reduced binding of the 5-HT2a receptor in the cortex of patients with schizophrenia. In a study of 30 drug-naïve patients with schizophrenia using PET with a 5-HT2a radio ligand there

was a negative correlation, among male patients, between 5-HT_{2a} binding in the frontal cortex and positive psychotic symptoms as well as significantly less binding of 5-HT_{2a} for both genders when compared with controls (Rasmussen et al., 2010). One study looking at 5-HT_{2a} receptor density in PFC post-mortem tissue of both patients and controls found an increase in binding sites, via [3H]ketanserin, in those who were not treated with antipsychotics, but had schizophrenia, compared with those who were treated with antipsychotics (Meana et al., 2012). However this study made the assessment of being antipsychotic-free based on negative results in post-mortem toxicology screenings; this was not indicative of being conclusively drug-naïve.

In a study looking at the effect of subchronic PCP treatment, via intraperitoneal (i.p.) injections, on DA and 5-HT receptor expression in the rat, Choi, Snigdha, Shahid, Neill, & Tarazi (2009) found that repeated treatment with PCP resulted in an increase in 5-HT_{1a} receptors in the medial (m) PFC and dorsolateral frontal cortex, with no significant alterations in any other regions. The same study found significantly decreased expression of D₁ receptors in both the medial and lateral caudate putamen, while the treatment failed to alter D₂, D₄, and 5-HT_{2a} receptor expression in all studied forebrain regions (Choi et al., 2009). It is interesting to note, however, that in human studies with participants that are at risk or in the prodromal phase of schizophrenia, there are reduced 5-HT_{2a} receptor densities in the DLPFC, posterior insular cortex, amygdala, hippocampus, and striatum (Choi et al., 2009). Postmortem studies have also shown reduced expression of 5-HT_{2a} messenger ribonucleic acid (mRNA) in the DLPFC, ACC,

hippocampus, and striatum (Kang, Huang, Wang, & Deng, 2009). The highlight provided through receptor autoradiography following PCP treatment is the downregulation of D1 and upregulation of 5-HT1a in the striatum and cortex, respectively, possibly adding to the neural basis for psychotic symptomatology like that seen in schizophrenia (Choi et al., 2009).

In studies with both monkeys and humans there has been a quantification of glutamatergic cells expressing 5-HT1a receptor mRNA in the PFC, wherein 80% of glutamatergic neurons, especially in layers two and three, expressed 5HT1a receptors in both species. In the same layers of the PFC about 13-21% of GABAergic cells expressed the 5-HT1a receptor, with numbers higher for humans but not significantly so when compared with counts from the brains of monkeys (de Almeida & Mengod, 2008). The complexity of interplay between receptor types and neurons from varying neurotransmitters is illustrated by these expressions. Numerous studies have also provided evidence of the benefits of combining selective serotonin reuptake inhibitors (SSRIs) with antipsychotic treatment in improving negative symptoms that are otherwise resistant to antipsychotic medication alone within as little as two weeks (Silver, Chertkow, Weinreb, Danovich, & Youdim, 2009). This result is somewhat perplexing seeing as the remedy to negative symptoms is due to serotonergic activity via SSRIs which are 5-HT agonists, yet clozapine, a 5-HT antagonist, is also effective despite the fact that the pharmacological profile of these two drugs combined predicts antagonism. However, clinical studies suggest that a combination of these two drugs may be more

effective in treating negative symptomatology than either one alone (Silver et al., 2009). The interplay amongst various neurotransmitters highlighted in the etiology of schizophrenia stresses the difficulty in developing targeted medications that take into account the complexity of these systems.

2.4 Antipsychotic Medications

As antipsychotic medications progress in terms of efficacy, safety, and tolerability better understanding of the neural mechanisms mediating their therapeutic effect will lead to still better treatments (Miyake, 2012; Westerink, 2002). The current state consisting of SGAs, representing first-line treatment, over FGAs, despite limited evidence of their superior effectiveness, and the advent of TGAs, whose efficacy over the former generations is yet to be elucidated in numerous ways highlights the limitations still faced in terms of treating schizophrenia. These limitations are represented on factors such as relapse prevention, vocational and social functioning, long term outcome, cognition, suicide prevention, quality of life and cost effectiveness when compared with previous generation antipsychotics (Miyake et al., 2012). The following section provides a brief review of the literature on risperidone, olanzapine, and aripiprazole.

2.4.1 Risperidone

Risperidone is an SGA and DA receptor antagonist and has been in clinical use since 1994. It is an antagonist at several adrenergic, 5HT, and DA receptor sites, except for D3 where it is an inverse agonist. Use of risperidone has been associated with risk of

cardiovascular disease and metabolic syndrome and when compared with FGAs can raise serum prolactin levels to equal amounts resulting in possible sexual side effects (Miyake et al., 2012).

Fujimura, Hashimoto, and Yamagami (2000) compared the effect of antipsychotics on Fos (an immediate-early transcription factor in neurons) protein expression in the rat. Those administered per-os (p.o.) risperidone, at 0.3 or 1.0 mg/kg, showed an expression unlike those injected with haloperidol, at 0.3 mg/kg, and most unlike those given clozapine. That is to say that this dosage did not affect the number of Fos protein-positive neurons in the mPFC, nucleus accumbens, or dorsolateral striatum, where only the latter two were positive with haloperidol, and all three positive for clozapine. However, a 3.0 mg/kg dose of risperidone revealed a significant increase in the number of Fos protein-positive neurons in all regions (Fujimura et al., 2000).

Robertson, Matsumura, and Fibiger (1994) looked at Fos-like immunoreactivity (FLI) in the rat brain, with subcutaneous (s.c.) injections at multiple doses of both FGAs and SGAs. An increase in neurons displaying FLI in the PFC was observed, however, this was not the case for all doses. SGAs, like clozapine, produced an increase in FLI in the medial striatum when doses were high enough (30 mg/kg compared with 10 mg/kg), whereas risperidone, and FGAs like haloperidol, produced an increase in FLI at all doses tested. Unlike haloperidol, risperidone had less of an effect in the lateral striatum.

Interestingly risperidone was the only medication, out of 17 others, that did not increase FLI in the lateral septal nucleus (Robertson et al., 1994).

In a study on procedural learning using the Tower of Toronto task (used to assess executive functioning with an emphasis on planning). Purdon, Waldie, Woodward, Wilman, and Tibbo (2003) found no significant effect from baseline after six weeks of treatment with risperidone, haloperidol, or olanzapine. However, at follow-up at the six month mark there was a significant decline in performance limited to those taking risperidone or haloperidol possibly implicating D2 receptor antagonism in the dorsal striatum as an explanation for this learning deficit (Purdon et al., 2003). One study doing a pre- and post-test of predictive saccades in drug-naïve patients with schizophrenia starting six weeks of treatment with risperidone, at 3.9 mg per day, found a marked decrease in accuracy after treatment when compared with healthy controls. However at the six-week mark, compared with baseline, there were no significant changes to dose, accuracy of sensory-guided, speeded or anticipatory saccades, or clinical symptom ratings (Harris, Wiseman, Reilly, Keshavan, & Sweeney, 2009). Meanwhile Reilly, Harris, Keshavan, and Sweeney (2006) did a pre- and post-test of first-episode patients with schizophrenia measuring memory for spatial locations in an oculomotor delayed response task. Prior to treatment with risperidone, patients showed impairments in working memory that increased over extended delay periods, e.g., one, two, four, or eight seconds, however, this impairment was intensified following six weeks of treatment with risperidone (Reilly et al., 2006).

Theory of mind involves the ability to identify thoughts, beliefs, knowledge, and intentions as being distinct for different people, and disparate from one's own. Using a

theory of mind (ToM) task Savina and Beninger (2007) found that patients with schizophrenia receiving SGA treatment, e.g., olanzapine or clozapine, performed similar to controls. This was excluding those on risperidone or taking an FGA, whose performance was worse than the other two groups on second-order false belief tasks. These tasks measure the ability to comprehend fixed mental states, and the faux-pas test requires awareness of discrepant information between speaker and listener. It is not clear whether olanzapine preserves or protects ToM from the degradation that occurs in schizophrenia or whether FGAs or risperidone impair ToM, as this has never been directly studied in prodromal individuals (Savina & Beninger, 2007).

Looking at the effect of long-acting injections of risperidone (27.0–37.5 mg bi-weekly) compared with other antipsychotics, e.g., haloperidol, flupenthixol, Surgaladze et al. (2007) used a sequential letter task requiring patients to use memory to select letters having appeared on a projector screen either one, two, or three letters back in a session that lasted approximately six minutes. The study was examining working memory by using functional magnetic resonance imaging (fMRI) to evaluate brain areas involved in processing working memory. Those taking antipsychotics other than risperidone showed over-activation of the VMPFC and under-activation of the ventrolateral (VL) PFC, while those taking risperidone, along with controls, showed a task-dependent decrease in the VMPFC suggesting a possible inhibition of this area given the lateral PFC is primarily responsible for driving successful performance in the task (Surgaladze et al., 2007). In a similar study, Honey et al. (1999) found that when patients were switched from FGAs to

risperidone, preceding a working memory task, during fMRI scanning there was increased activation of the right PFC associated with improved performance when compared with those on FGAs. Risperidone's efficacy as a treatment for schizophrenia has been well documented in the literature, at least with regard to positive symptoms; however, inconsistencies in its ability to attenuate certain impairments (e.g. learning deficits) not present with other SGAs make it, in some ways, an inferior treatment.

2.4.2 Olanzapine

Olanzapine is an SGA medication first approved for oral use in 1996. Olanzapine has a higher affinity for 5-HT₂ receptors than D₂ receptors and it functions as both an antagonist and inverse agonist. Olanzapine has been associated with numerous side effects that pose a risk toward developing cardiovascular disease or metabolic syndrome, including weight gain, hyperlipidemia, and hyperglycemia (Miyake et al., 2012).

In an eight-week study by Stip et al. (2003) looking at neuropsychological functioning at three time points (baseline, four weeks, and eight weeks) in patients with schizophrenia it was found that after switching from both FGAs and other SGAs to olanzapine, 10 mg per day in the first week, subsequently adjusted to between 5 and 20 mg per day, there was a significant improvement. Improved functioning on the Rey Auditory-Verbal Learning, Controlled Oral Word Association, Category Instance, and Trail Making Tests was observed with the most notable ameliorations occurring in learning and memory (Stip et al., 2003). Meanwhile Schlagenhaut et al. (2008) used fMRI to observe regions of interest in patients with schizophrenia as they performed a

working memory task both at the time of taking FGAs, e.g., haloperidol, and again after being switched to olanzapine. As expected at both time points, patients had less correct responses when compared with controls, however, there was little significant change in the blood oxygen level-dependent (BOLD) signal in parietal or frontal regions during working memory performance when patients were switched from FGAs to olanzapine. It is worth mentioning that patients taking FGAs in this study had been treated for as little as two weeks at first scan, and although the second scan came at four weeks from this time point, patients switched to olanzapine had been on this medication for as little as two weeks with overlap in their FGA treatment (Schalgenhauf et al., 2008).

A six-week double-blind randomized trial was carried out by Revicki, Genduso, Hamilton, Ganoczy, and Beasley (1999) to assess the efficacy of olanzapine, compared with haloperidol, in improving quality of life, as measured by the quality of life scale (QLS), positive and negative syndrome scale (PANSS), and brief psychiatric rating scale (BPRS), for patients with schizophrenia. Significant improvement was observed with those taking olanzapine vs. haloperidol and those individuals who showed tolerability and response to the medication entered into a 46-week double-blind extended trial. The result was attenuation of negative symptoms and improved quality of life for those taking olanzapine, where withdrawal from treatment, and the study, by those taking haloperidol, due to adverse outcomes, was significant (Revicki et al., 1999). Quite contrary to these results, in a double-blind randomized controlled trial (RCT) of patients with schizophrenia treated with either olanzapine or haloperidol, Rosenheck et al. (2003)

found that olanzapine was no more effective than haloperidol on most of the factors studied (symptomatology, EPS, quality of life); however, it conferred a slight benefit over haloperidol in terms of motor function and memory. Numerous assessments occurred over the course of a year, starting at baseline and several neuropsychological tasks were used to assess functioning, with one notable exception to olanzapine over haloperidol in that it was associated with more frequent reports of weight gain (Rosenheck et al., 2003). Reports of olanzapines efficacy in treating schizophrenia symptomatology are varied and further research is needed to delineate not only its function as a treatment but its performance compared with other antipsychotic medications.

2.4.3 Aripiprazole

Aripiprazole, or Abilify, is unique among antipsychotic medications in that it is a partial DA agonist, with an affinity for D2 and D3 receptors. In animal models of DA hyperactivity and hypoactivity, aripiprazole exhibits the characteristics of a functional antagonist and agonist, respectively, and it acts on both presynaptic autoreceptors and postsynaptic D2 receptors (Argo, 2004; Miyake, 2012). It binds to approximately 90% of striatal D2-like receptors at clinical doses and causes few EPS. Furthermore, aripiprazole demonstrates partial agonism and antagonism of the 5-HT1a and 5-HT2a receptors, respectively, along with moderate affinity for adrenergic ($\alpha 1$), histaminergic (H1), 5-HT6, and 5-HT7 receptors, with negligible affinity for D1 or muscarinic receptors (Argo, 2004; Miyake, 2012).

In one preclinical study, aripiprazole improved impairments to memory via 5-HT1a receptor activation in a glutamate receptor antagonist model of schizophrenia. In one 5-day RCT aripiprazole, at a mean dose of 19.3 mg/day, was found to be as effective as olanzapine, at a mean dose of 20.0 mg/day, at treating agitation in severely ill patients with schizophrenia. A similar four-week RCT looking at both aripiprazole, at 15.0 mg/day, and risperidone, at 6.0 mg/day, in people with schizophrenia or schizoaffective disorder, found a significant amelioration occurred for both medications as measured by the PANSS. Aripiprazole has been associated with less adverse side effects including drowsiness, weight gain, cholesterol, triglycerides, and prolactin levels, when compared with olanzapine. A similar comparison of side effects is found when compared with risperidone; however, the aripiprazole group had a higher occurrence of tremors (Miyake, 2012; Potkin, 2003).

In an eight-week study looking at the effect of switching patients with schizophrenia from their normal FGA medications (haloperidol) and SGA medications (olanzapine, risperidone) to aripiprazole, Casey et al. (2003) found a preserved and in some cases a slightly improved disposition with regard to symptomatology as measured primarily by the PANSS, and clinical global impression scale (CGI). Patients were assigned to three groups: those who were transferred to aripiprazole (30 mg/day) concomitantly with either immediate cessation of their prior medication, tapering off their prior medication over two weeks, or gradually increasing dosage of aripiprazole to 30 mg/day whilst tapering off use of prior medication over a two-week period. All treatment

groups responded positively to the change with comparable profiles of functioning and safety (Casey et al., 2003). In a four-week study, also using the PANSS and CGI, Potkin et al. (2003) compared dosages of aripiprazole (20 vs. 30 mg/day) risperidone (6 mg/day) and placebo in patients with schizophrenia or schizoaffective disorder. Potkin et al. (2003) found the placebo group to have the worst scores on all measures, with both dosages of aripiprazole resulting in significant improvements as early as one week after the initiation of the trial when compared with placebo. Both aripiprazole and risperidone were comparable in terms of improved functioning over placebo (Potkin et al., 2003).

In a longitudinal study using fMRI, attempting to assess working memory in patients with schizophrenia who were switched from an FGA to aripiprazole, Schlagenhauf et al. (2010) found an increase in the BOLD signal in the dorsal part of the ACC (involved in executive control of behavior) when patients were switched to aripiprazole. Furthermore a reduced signal in several areas of the PFC was observed in patients when compared with healthy controls. In each scan participants performed a task requiring them to match either a number seen two numbers back, that was currently on the screen, or identify a zero anytime it appeared by pressing a button. Importantly, patients had been on typical treatment for as little as two weeks at the time of first scanning, and on aripiprazole for as little as three weeks at the time of the second scan (Schlagenhauf et al., 2010). Research has been promising with aripiprazole due in part to its unique pharmacological profile, however the inability of aripiprazole to supersede previous generations of antipsychotics outlines the challenges still faced by researchers.

2.5 Multiple Memory Systems

Two major divisions of memory consist of declarative, or explicit, and NDM, or implicit memory. The latter involves non-conscious skill acquisition or procedural learning and is the focus point of the two NDM tasks used in this study. The former involves consciously learnt and recalled information. There are three primary systems pertaining to declarative memory that have been distinguished as a result of lesion studies with animals and both neuropsychological and neuroimaging studies with humans. These systems are episodic, semantic, and modality specific (Henson & Gagnepain, 2010). Episodic memory involves representing associations between objects in spatial and temporal contexts, supported primarily by the hippocampus. Semantic memory is involved in obtaining information about characteristics that describe objects, dependent on the anterior temporal cortex. Lastly, modality specific perceptual systems characterize the sensory features of stimuli, dependent on higher sensory cortices. However an interaction among these three systems underlies the function of declarative memory in the brain (Henson & Gagnepain, 2010).

It was at the beginning of the 19th century when science started to investigate where memories are stored in the brain arising with presumptions put forth by Franz Joseph Gall. Gall rejected mind-body dualism in favour of a purely materialistic explanation and proposed cortical localization, emphasizing that the brain is divided into different faculties, each corresponding to a specific mental function (Milner, Squire, & Kandel, 1998). Experimental research challenged phrenology and the notion of cortical

localization for specific behaviours well into the first half of the 20th century. On the heels of work by Karl Lashley, Donald Hebb explored the idea in his 1949 book, “*The Organization of Behaviour*” that cell assemblies, not single brain regions, are responsible for learning and memory (Milner et al., 1998). Since lesions leave numerous connections among these assemblies intact the theory made sense in explaining how information could remain represented despite site-specific damage. The work of Wilder Penfield and Brenda Milner provided direct correlations between cognitive deficits and damage or ablation to specific areas of the brain, most famously with patient H.M. It is true that if an area of damage is large enough it may sever all connections within a given cell assembly. In fact, the work with patient H.M. provided evidence of intact motor skill learning, despite other deficits, and gave rise to a plethora of related experiments that carved out the veracity of multiple memory systems. (Milner, 1998; Saint-Cyr, 1988; Squire, 1986).

Spatial response maze tasks, like the water maze or radial maze, are often used to study spatial learning and memory in animals. Experiments with rats in spatial response maze tasks has suggested that many neurons, in the hippocampus and striatum, reacting to information about location, movement, or reward, show similar firing patterns regardless of changing cognitive demands (Mizumori, Yeshenko, Gill, & Davis, 2004). This suggests a system of reference for information in a spatial context, in the hippocampus, and a sensory context for the striatum, comparing learned expectations with actual outcomes; however, both systems appear to work through parallel processing despite having distinct anatomical regions creating implications for our understanding of

multiple memory systems (Mizumori et al., 2004). Understanding how neural systems underlying learning and memory interact is critical in being able to inform better treatment of neuropsychiatric disorders, especially those in which decision making is negatively affected by either the disorder or its treatment (Delgado & Dickerson, 2012).

In 1980, the work Neal Cohen and Larry Squire did with amnesic patients provided evidence of dissociations in how we use memory, giving credence to declarative and NDM processes. Declarative memory is dependent on the medial temporal lobe and is involved in the conscious act of representing the external world and storing information about facts and episodes (Milner et al., 1998). Non-declarative memory however characterizes the ability to react properly to stimuli through practice consequent to conditioning or habit learning, yet is removed from conscious inference. Subsections of non-declarative memory functioning include: priming, wherein exposure to a stimulus affects a response to a later stimulus, an ability preserved in amnesic patients despite lack of conscious awareness; habit memory, dependent on the caudate nucleus; emotional learning, dependent primarily on the amygdala; and Pavlovian conditioning, dependent on the cerebellum (Milner et al., 1998).

Experimental research with non-human primates indicates that there may be multiple working memory domains within the PFC, each with its own specialized method of processing storage of distinct content and organized in separate parallel anatomical networks (Goldman-Rakic, 1997; Squire, 1986). In patients with schizophrenia several pathologies have been found in cortical and subcortical brain areas associated in

significant ways with the PFC. Among cortical areas these involve the ACC, posterior part of the cingulate cortex, superior temporal gyrus, and the medial temporal areas. Among subcortical areas the nucleus accumbens, neostriatum, and medial dorsal nucleus of the thalamus are of importance (Goldman-Rakic, 1997; Squire, 1986).

Using fMRI to study implicit learning in patients with schizophrenia treated with SGAs, Reiss et al. (2006) found an under-activation of the striatum during the serial reaction time (SRT) task when compared with healthy controls. Moreover, with the SRT task Stevens et al. (2002) showed that patients taking the SGA, olanzapine (10-20 mg/day), for as little as two weeks, had comparable performance to controls in terms of implicit learning, and superior performance on implicit learning and psychomotor speed when compared with patients taking FGAs, e.g., haloperidol (>5 mg/day).

Using fMRI, Purdon, Waldie, Woodward, Wilman, and Tibbo (2011) investigated differences between healthy controls and patients with schizophrenia in procedural learning using the SRT task. Patients were first-episode, drug-naïve, and comparable to controls in activations of the ACC, subcortical structures, and numerous left frontal structures; however, they had less activity in one section of the left middle frontal cortex on procedural trials when compared with controls, suggesting a possible location of impairment in the disorder prior to treatment (Purdon et al., 2011). Using the mirror drawing task to study procedural learning, Scherer et al. (2004) found that patients with schizophrenia treated with SGAs such as clozapine and risperidone did not show the kind of impairment seen in those treated with haloperidol; however, this difference was most

pronounced in the clozapine group. The differential effects of FGA and SGA medications on both explicit and implicit memory are well documented; however, much research is needed to discern the precise manner in which these systems function and respond to drug treatment.

2.5.1 Iowa Gambling Task

Appraisal of the risks and benefits within any situation relies on cognitive and emotional substrates (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005). The IGT has been extensively used to evidence cognitive impairments in numerous disorders, including schizophrenia, although the neural foundations for performance in this task have yet to be fully explained (Bechara, 1997; Fukui, 2004).

Prefrontal damage poses the greatest difficulty for participants performing the IGT as success in the task relies upon decision making, risk assessment, and NDM (Bechara et al., 1997). Participants are presented with four decks of cards on a computer screen wherein they are asked to select from any deck they choose. Participants are provided with \$2000 in virtual money that they can augment through reward payoffs that come with each deck. However, each deck also comes with an unknown penalty that is decidedly more severe in some decks vs. others. Learning over trials is dependent on a shift toward selecting those decks which come with less severe penalties (Bechara et al., 1997).

Bechara et al. (1997) found that patients with damage to the PFC failed to learn the value of going for the advantageous decks when compared with healthy controls that

learnt to pick the favourable decks before conscious awareness of such strategy. This was inferred through intermittent breaks, at 10-card intervals, wherein subjects were asked questions about their thoughts on what was happening along with how they felt about it. Despite the lack of conscious awareness about what healthy participants were doing, evidence for non-declarative learning was further corroborated by anticipatory galvanic skin responses (GSRs). Interestingly, even after consciously learning the correct strategy, patients with damage to the PFC continued to make unfavourable choices (Bechara et al., 1997). In a similar study Bechara, Damasio, Damasio, and Lee (1999) looked to dissociate the role of the VMPFC and the amygdala in decision making in the IGT. Patients with bilateral damage to each structure failed to show anticipatory GSRs when thinking about risky choices; however, those with damage to the VMPFC alone did show a response when faced with an actual punishment or reward, implicating emotional deficits in decision making in this task, although when compared with controls both patient groups failed to show learning by switching to the advantageous decks (Bechara et al., 1999).

Looking at the performance of healthy controls on the IGT, undergoing fMRI, Fukui et al. (2004) found a significant activation in the mPFC, specifically the medial frontal gyrus alone, when comparing risky decisions vs. advantageous ones. Seeing as intact performance in the IGT was dependent on the mPFC alone this study provides supporting details about the deficits seen by Bechara et al. (1999). Finally, Wasserman et al. (2012) have shown that patients with schizophrenia, or schizoaffective disorder, taking

FGAs, e.g., haloperidol or risperidone, performed better in terms of learning over trials on the IGT, than patients taking olanzapine or clozapine. The control group performed better than both patient groups, and seeing as though the IGT relies on an intact PFC and SGAs often affect the mPFC and nucleus accumbens this finding is in line with other research (Bechara, 1999; Wasserman, 2012). Although there is some discussion in the literature over the efficacy of this task, along with disagreements as to the best way to set it up, the IGT has been an established tool for evaluating impairments to the PFC.

2.5.2 Weather Prediction Task

Swift classification of both novel and familiar information is required under numerous circumstances in our environment and it is thought that such learning requires multiple memory systems (Price et al., 2009). The WPT is a probabilistic classification learning task wherein subjects are presented with varying combinations of cards with differing geometric shapes and colours that are used to inform outcomes of good or bad weather. As each geometric shape is associated with a probability toward either outcome, the learning comes in being able to detect which outcome is likely when seeing that shape and colour (Gomar et al., 2010; Wasserman et al., 2012). Complicating this is the fact that in any given trial combinations of cards are presented forcing the participant to develop, using non-declarative memory, a representation of those probabilities associated with likely or unlikely weather outcomes.

In a study comparing the performance of people with schizophrenia, and schizoaffective disorder, on the PCL, Wasserman et al. (2012) found that those patients

taking the SGA, clozapine, but not olanzapine, risperidone, or FGAs, showed improved learning over trials; however, it is noteworthy to mention that those taking clozapine had a poorer start in the first trial block when compared with the other medication groups. Comparing people with schizophrenia taking either FGAs, SGAs, or both, and healthy controls on a number of procedural learning tasks including the PCL, Gomar et al. (2010) found that although patients started with only a slightly poorer performance, as trials progressed the disparity between groups expanded with patients having a subordinate performance when compared with controls, revealing significance between group and trial block.

Looking to differentiate the explicit and implicit features of performance on the PCL, Price et al. (2009) had undergraduate university students complete the task under different time scales of feedback so as to delay time to information about performance to impact non-declarative functioning, and shorten it such that there was little time to explicitly register how one was doing. Interestingly, delayed feedback had little effect on performance; however, shortened feedback time resulted in significantly fewer optimal responses suggesting a possibly strong declarative component to this task (Price et al., 2009). Contrary to this finding, Seger and Cincotta (2005) found increased activity in the body and tail of the caudate nucleus, involved in habit memory, and decreased activity in the hippocampus, important for conscious recollection, when correlations with successful learning were made in the PCL under fMRI analysis, suggesting a dependency on non-declarative functioning for success in the task. Furthermore, Gluck, Shohamy, and Myers

(2012) investigated the ways in which individuals approach the task and found that there are three main strategies. Multi-cue strategies employ focus on all four cues, singleton strategies involve figuring out a reliable pattern based on the appearance of a single card, and one-cue strategies wherein participants react based on a single cue; however, the list of strategies they studied was not exhaustive leaving room for other adaptive methods to learning this task (Gluck et al., 2012). Disputes in the literature over whether the PCL is in fact measuring NDM are worth consideration; however, this task has been well validated and used extensively in studies of NDM and disorders affecting the striatum.

2.6 Rationale and Hypothesis

Previous studies have dissociated multiple systems for processing different types of memory, e.g., NDM vs. DM, that depend upon anatomically distinct brain regions, e.g., the mPFC and striatum. NDM performance has previously been shown to be impaired in people with schizophrenia taking antipsychotic medications. The goal of the present study was to assess NDM using the IGT and PCL in groups of patients with schizophrenia treated with olanzapine. We tested the hypothesis that patients with schizophrenia treated with olanzapine would have a poorer performance on the IGT, but not the PCL, when compared with controls. As results with olanzapine in previous research have been inconsistent, the present study sought to establish a performance profile in patients taking this SGA. We also hypothesized that performance of patients taking aripiprazole would be comparable to those taking risperidone, or an FGA; however, we were unable to recruit a sufficient amount of participants to test this

hypothesis. A small number of participants who were taking aripiprazole, risperidone, or more than one antipsychotic drug, were included to provide a preliminary look at the performance of these individuals on the two tasks. The novel TGA aripiprazole has a marked affinity for D2/D3 receptors and the affinity for the D2 receptor surpasses that for 5-HT receptors by an order of magnitude (Miyake et al., 2012). FGAs, unlike SGAs, have higher affinity for the D2 receptor, whereas SGAs have a higher affinity for 5-HT receptors. Considering that risperidone has pharmacological action like that seen with FGAs and affects the dorsal striatum, altering performance on the PCL, whereas SGAs typically affect the PFC and alter performance on the IGT, a future goal extending from preliminary findings in the present study will be to test the hypothesis that aripiprazole will result in a pattern of performance like that seen in risperidone.

Chapter 3

Materials and Methods

3.1 Participants

Inpatients and outpatients had a diagnosis of either schizophrenia or schizoaffective disorder. Participants were excluded if they had been taking their medication for less than a month, used a non-prescribed psychoactive substance in the 24 hours prior to testing, were under 18 years of age, had had a traumatic brain injury, or had a history of, or present, gambling addiction. Control subjects were excluded if they had a mental illness diagnosis, had suffered a traumatic brain injury, used a psychoactive substance 24 hours prior to testing, were under 18 years of age, or had a history of, or present, gambling addiction. Comparison between the control group and those patients taking olanzapine was primarily sought, alongside preliminary probes into the performance of patients taking aripiprazole or risperidone. Groups (n) were: students (26) olanzapine (12), aripiprazole (2), risperidone (2), and controls (16). Polypharmacy groups included risperidone/olanzapine (2) and risperidone/aripiprazole (1). Duration of illness and use of medications other than antipsychotic drugs was not systematically recorded. Control and patient groups were matched for age, sex, and education. Initial power analysis was as follows: $(2.80/.50)^2 = 5.62$, resulting in 31 people for each group. This would result in 93 people with schizophrenia and 31 controls; however, challenges were faced in finding this many participants.

3.2 Medications

Only patients taking olanzapine (Zyprexa), aripiprazole (Abilify), or risperidone (Risperdal) were included in the study. Three participants were taking combinations of these medications and their data were included but not analyzed. Numerous patients were being treated with other medications for metabolic disorders, mood disorders, or other conditions. All participants were advised to be free of any psychoactive drug use (beyond prescribed medicine) 24 hours prior to commencement of testing.

3.3 Materials

Participants were brought to a private room for testing and were given a letter of information and consent form along with a brief dialogue about the details of their participation before any testing initiated. Participants were then questioned for demographic information followed by two questionnaires for assessing psychiatric symptomatology and cognitive functioning, the BPRS and the MMSE, respectively. Participants then went on to perform the PCL and IGT. The WPT created by Gluck and Bower (1988) has seen considerable use in recent years (e.g., Wasserman et al., 2012). Participants sat in front of a laptop computer along with brief instructions provided by the investigator, as well as on-screen instructions. For the PCL, participants were shown combinations of cards, each with its own geometric shape and colour and asked to select one of two outcomes based on the pattern of cards before them on the screen (Fig. 1). Two keys on the bottom left and right of the screen were selectable for a rainy weather outcome, imaged by a cloud, and a sunny weather outcome, imaged by a sun,

respectively. Following an incorrect or correct response participants would see their choice of a rain cloud or sun appear at the top accompanied by either a low frequency tone (0.5 sec) and non-smiling face or a high frequency tone (0.5 sec) and a smiling face, respectively. After 5 seconds the next trial commenced and there was a 20-second break period after each block of 25 trials. Probabilities were 25, 43, 57, and 75% and different cards were correlated with each probability for each participant. Participants were not informed that the cards were probabilistically associated with outcomes until the end of the study.

Instructions on screen directed participants to press either the rain key, appearing in the bottom left of the screen, or the sun key, appearing in the bottom right, to begin. On-screen instructions were as follows: “in this game you are the weather forecaster. You will learn how to predict rain or sunshine using a deck of four cards. On each turn you are dealt one, two, or three cards”. Participants were then shown two different cards side by side and asked, “Do you think these cards predict rain or predict sunshine? Make your choice by pressing the Rain key or the Sun key”. Following their selection participants were given feedback on-screen saying, “The actual weather on the next day is displayed. In this case your forecast was correct so you hear a high beep and see a happy face”. This introduction allowed for a brief trial run to familiarize participants with the rules of this task. Participants then read, “Each time new cards are dealt, examine them; then make your forecast by pressing the Rain or the Sun key”. Participants made a selection and with a new screen read, “The actual weather follows your forecast. In this case you were

wrong so you hear a low beep and see a not-so-happy face”. A new screen appeared showing the four cards with geometric shapes consisting of blue squares, yellow triangles, red circles, and green diamonds, asking “ready?” and so the task began.

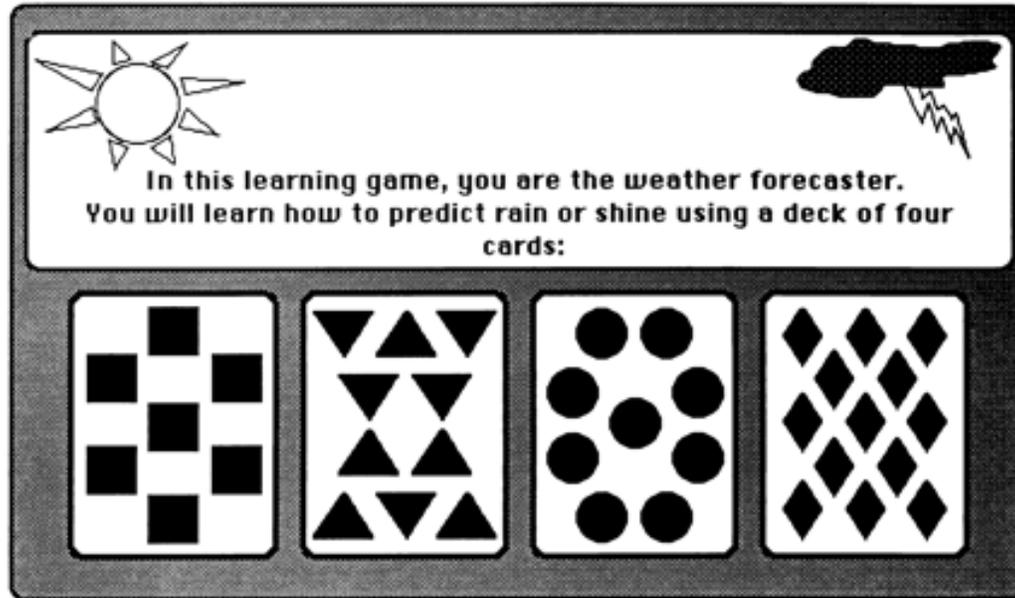


Fig. 1 Example of computerized probabilistic classification learning task. Actual screen background was black with colours for each geometric shape on the cards (Squire & Zola, 1996).

The IGT as described by Bechara et al. (1997) involves learning to make less risky decisions by selecting “good” decks over “bad” decks out of four decks that come with infrequent penalties of varying severity. The IGT has been shown to rely on NDM, in that healthy participants move toward selecting from the good decks before being consciously aware of the differential risk associated with them (Bechara et al., 1997).

Participants sat at a laptop computer and on-screen instructions read the following: “You are about to take part in an experiment that involves gambling with play

money. You will start with a \$2000 loan. On each trial, you will select a card from one of four decks. After you select each card, you will be given a reward and possibly be required to pay a penalty. Your goal is to maximize the profit on your loan, and you may choose from any deck at any time to do so. Click the mouse to continue”. A new screen appeared with the following written instructions: “For each card you draw, you will get a reward. This reward depends on the deck you choose, and each deck has a fixed reward. You will also get a penalty, which will cost you money. Penalties are somewhat random—the penalty you will get is different for different cards in the deck. Sometimes the penalty will be zero, and sometimes it will be larger, at times even larger than the reward you get for choosing that deck. You should try to get as much money as possible by the end of the study. Press the mouse to continue”. A new screen appeared with the following instructions: “At the bottom of the screen, there is a graph which shows you your current earnings. The more money you have, the larger the bar will be. Now you will begin the test. Do you have any questions? Press the mouse to begin”.

Participants were then shown a new screen with 4 decks of cards along the top below a title in bold black lettering that said to select the deck by clicking with the mouse (Fig. 2). Each deck was numbered one through four, and displayed below the cards in bold black lettering was the total amount of money earned. Below that was a bar ranging from \$-10000 to \$5000 with five notches in between including 0, 1000, 2000, 3000, and 4000. To the left of where the total was displayed was information pertaining to each selection consisting of ‘choice’, identifying deck number, ‘reward’, delineating the pay

off, 'penalty', denoting the loss, and 'net gain', outlining the resulting amount between the two. Choices that resulted in earned money were in green, those that lost more money than was earned were in red, and those that broke even were in black. Subjects were thanked for their participation upon completion of the task and provided with answers to any questions they had by the investigator. Participants were provided with a debriefing form explaining the purpose and function of each task and compensated \$10/hr.

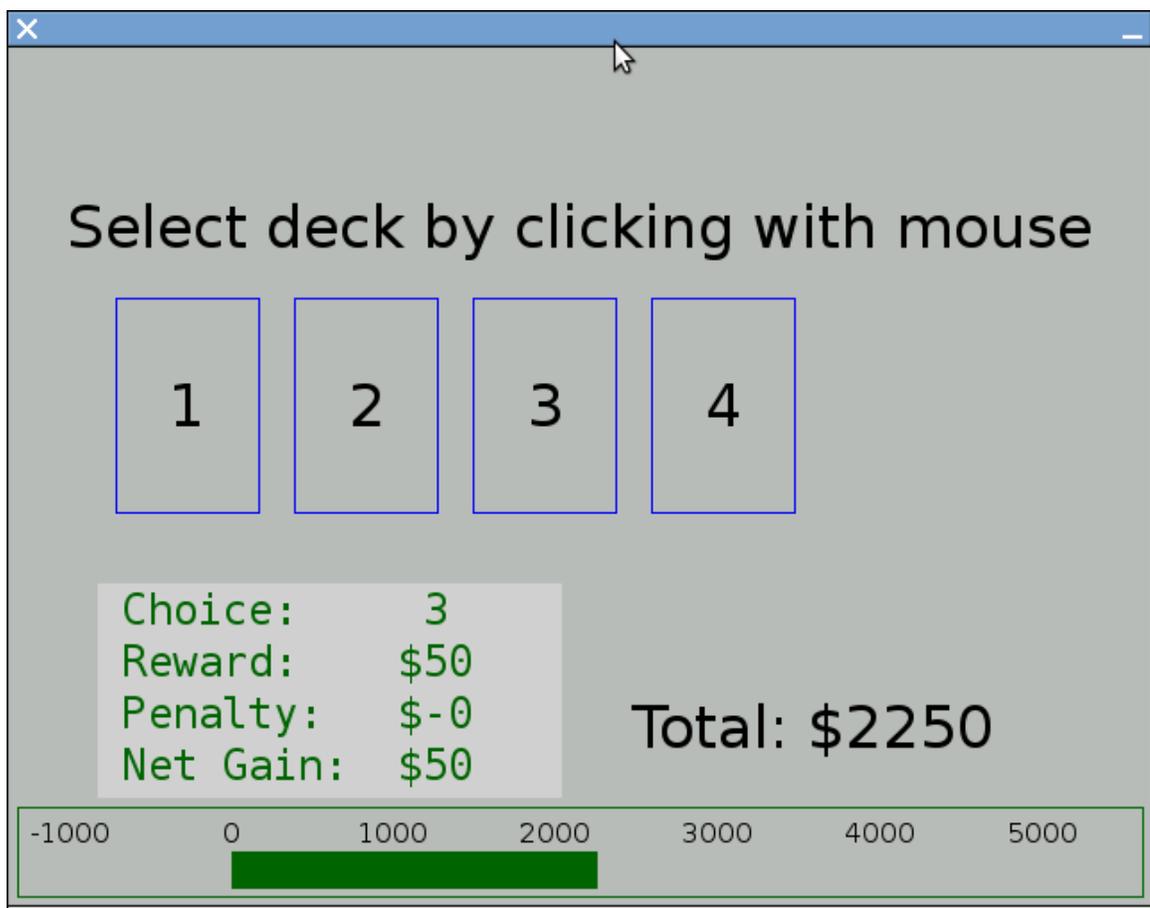


Fig. 2 Screen shot of the computerized Iowa gambling task displaying what participants saw (Mueller, 2012).

3.4 Procedure

A pilot study was carried out to evaluate performance on the PCL and IGT in a non-clinical control group. The pilot study began through an email notification sent out through various departments to grad students at Queens University.

Recruitment of patients with schizophrenia treated with antipsychotic medications took place at Providence Care Mental Health Services, Frontenac Community Mental Health Centre, both located in Kingston, Ontario, and Waypoint Mental Health Centre, located in Penetanguishene, Ontario. Recruitment began with the principal investigator (P.I.) creating a short list of candidate participants from information obtained from the pharmacy on site. The P.I. made first contact with doctors through email, and then in person, for permission to access their medical database and patients. Administrative approval was obtained through research ethics clearance and meetings with management on different wards at each facility.

The P.I. worked with staff to notify potential participants about the study and attain consent for future contact with candidate subjects. The P.I. arrived at scheduled times to meet with individual patients who were given necessary guidance and information with regard to what the experimental session entailed. Once written and informed consent had been obtained patients were administered both the BPRS and the MMSE to assess schizophrenia symptomatology and level of cognitive functioning, respectively. Afterwards patients were given the PCL and the IGT; the two tasks combined ran an approximate time of 45 minutes. Recruitment of controls took place

alongside recruitment of patients in an attempt at demographic matching, e.g., sex, age, education. Controls were contacted through ads placed online and around the community. This study was granted clearance according to the recommended principles of Canadian ethics guidelines, and Queen's policies, with clearance from the General Research Ethics Board (GREB), and the Health Sciences Research Ethics Board (HSREB).

3.5 Data Analyses

Analysis of variance (ANOVA), $\alpha = 0.05$, were used to compare groups on the MMSE and BPRS scores, as well as demographic information including age, sex, and education. Education was scored on a Likert scale so that participants with an education at the elementary, high school, undergrad, masters, and PhD level, received a 1, 2, 3, 4, or 5, respectively. Group means over trial-blocks of 20 were compared using ANOVA. For both tasks, two sets of ANOVA were performed, one-way repeated measures for each group and two-way mixed design, with independent groups and repeated measures of blocks for group comparisons. Number of selections from individual decks in the IGT task was evaluated using group by trial-block ANOVA. One-way ANOVA were carried out for each of the three main groups (students, controls, and olanzapine) to assess individual performance on the two non-declarative memory tasks (PCL and IGT), demographic information, and scores on the two questionnaires (MMSE and BPRS). Comparisons in performance between controls and students, and then the olanzapine group and controls, were made using two-way repeated measures. Those taking

risperidone, aripiprazole, or a combination of either with olanzapine, were excluded from the analysis due to an insufficient sample size in each group.

Chapter 4

Results

4.1 Data Analyses

Table 1: Participant characteristics

	Students	Controls	Olanzapine	Risperidone	Aripiprazole	Ola/Ris	Ris/Ari
n	26	16	12	2	2	2	1
Gender	8M, 18F	8M, 8F	11M, 1F*	1M, 1F	1M, 1F	2M	1M
Age	22.15 ± 1.75	50.56 ± 2.77	38.83* ± 2.78	39.00	38.5	41.5	27
Education	4.46 ± 0.35	2.25 ± 0.17	1.75* ± 0.13	1.50	3	3	2
PCL total (for 100 trials)	52.34 ± 4.05	49.38 ± 3.95	43.91* ± 2.91	50	47	40	33
IGT total (for 100 trials)	54.07 ± 4.58	52.45 ± 4.62	57.91 ± 5.22	55	43	55	42
MMSE	n/a	29.44 ± 0.16	22.75 * ± 2.23	14.50	30	23.5	24
BPRS	n/a	23.94 ± 0.90	55.92 * ± 7.00	n/a	50	60	23

A table displaying the breakdown of group means (\pm SEM) across all measures. * Different from controls ($p < 0.05$) following significant analysis of variance. Abbreviations: Ari, aripiprazole; BPRS, Brief Psychiatric Rating Scale; F, female; IGT, Iowa Gambling Task; M, male; MMSE, Mini Mental Status Examination; Ola, olanzapine; PCL, Probabilistic Classification Learning; Ris, risperidone.

4.1.1 Demographics and Questionnaires

Demographic data (Table 1) were compared in a one-way ANOVA between the olanzapine group and controls wherein there was a significant main effect of education,

$F(1, 27) = 4.82, p < .037$, gender, $F(1, 27) = 6.29, p < .019$, and age, $F(1, 27) = 8.55, p < .007$. Comparisons between the olanzapine group and controls revealed significant differences in scores on the MMSE, $F(1, 26) = 12.04, p < .002$, and the BPRS, $F(1, 26) = 27.38, p < .001$. Performance on the MMSE is measured along a 30-point rating scale, wherein a lower score signifies an increasing decline in cognitive functioning. The BPRS assesses psychiatric symptomatology, and uses Likert scoring to rate the severity of each symptom, so that a higher total score reflects more severe symptoms.

4.1.2 Student Performance in Pilot Study for PCL and IGT

Before any testing occurred with patients or the control group from the general population, a pilot study was conducted with students ($n=26$) from Queens University to evaluate learning on the PCL and the IGT. Learning was observed in both tasks. ANOVA of within-subjects effects revealed a significant main effect of block on the PCL, $F(4, 25) = 3.22, p = .016$, (Fig. 3), and the IGT, $F(4, 25) = 4.60, p = .002$ (Fig. 4).

4.1.3 Control Group Performance on PCL and IGT

A one-way ANOVA was run on the control group ($n=16$) before comparisons with the olanzapine group to assess their learning of the two tasks. The control group only approached significance in the PCL task, $F(4, 75) = 2.20, p = .077$ (Fig. 3), while displaying normal learning in the IGT, $F(4, 75) = 2.65, p = .040$ (Fig. 4).

4.1.4 Olanzapine Group Performance on PCL and IGT

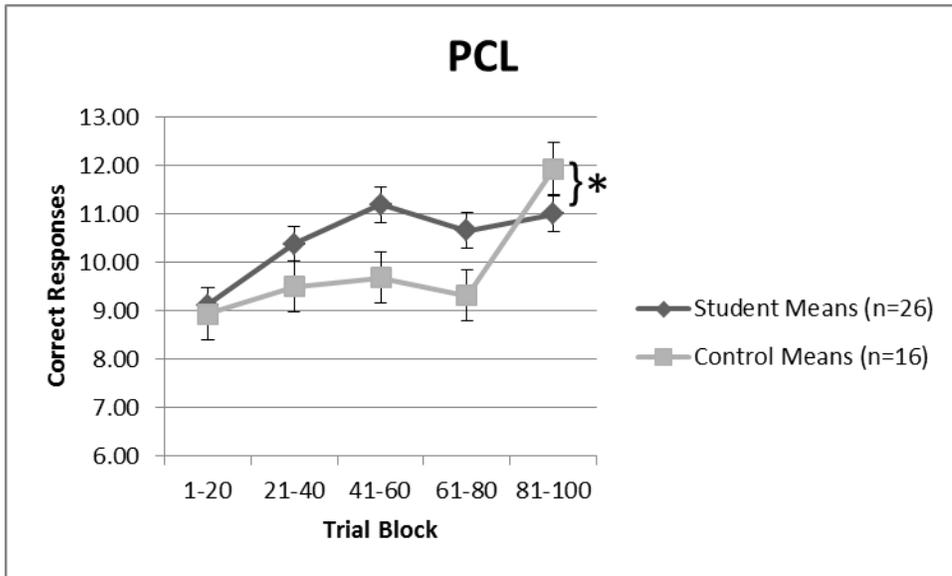
Each participant in the olanzapine group had been on this medication for at least one month prior to inclusion in the study. A one-way ANOVA revealed that the olanzapine group had some trouble learning the PCL, $F(4, 55) = 4.77, p = .379$ (Fig. 5), and IGT, $F(4, 55) = 1.63, p = .178$ (Fig. 6).

4.2 Students vs. Controls on PCL and IGT

On the PCL, performance of both the student and control groups improved from the first to the fifth trial block, but the control group appeared to improve later than the student group, suggesting a group by trial block interaction (Fig. 3). However, ANOVA revealed only a significant main effect of block, $F(4, 40) = 5.40, p < .001$, the group effect, $F(1, 40) = .788, p = .380$, and interaction, $F(4, 40) = 1.70, p = .151$, being non-significant. Statistical results suggest that the performance of the student and control groups was similar on the PCL.

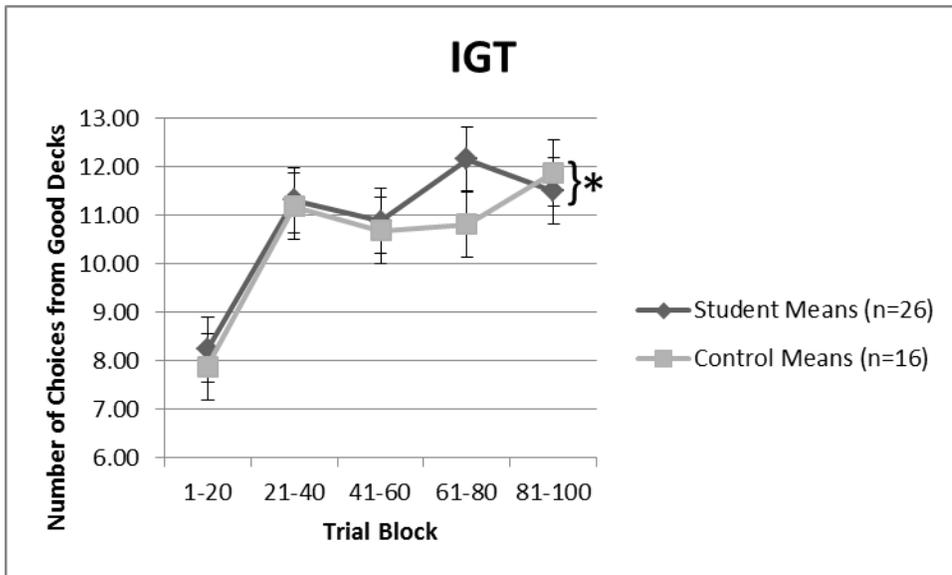
Both groups appeared to learn the IGT at about the same rate (Fig. 4). ANOVA revealed a significant main effect of block, $F(4, 40) = 6.66, p < .001$, with a non-significant group effect $F(1, 40) = .123, p = .728$, and interaction, $F(4, 40) = .296, p = .880$, suggesting both groups learnt the IGT in a comparable way.

Figure 3: Performance on the Probabilistic Classification Learning (PCL) Task



*Asterisk indicates a significant block effect in a group by blocks analysis of variance.

Figure 4: Performance on the Iowa Gambling Task (IGT)



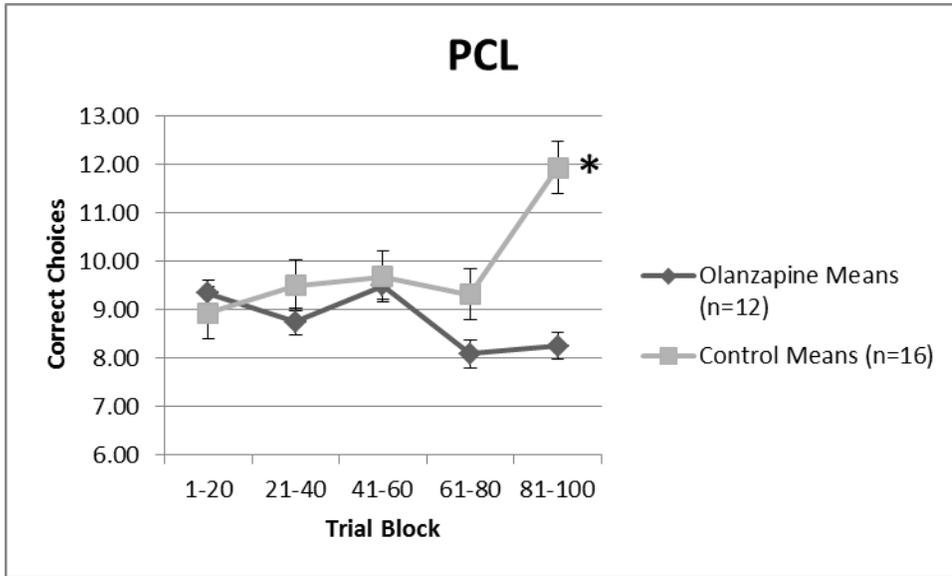
*Asterisk indicates a significant block effect in a group by blocks analysis of variance.

4.2.1 Olanzapine vs. Controls on PCL and IGT

As discussed in the previous section, the control group appeared to learn the PCL by the fifth trial block; the olanzapine group showed little evidence of learning (Fig. 5). This description of PCL performance was supported by the results of ANOVA that revealed a significant interaction, $F(4, 26) = 3.09, p = .019$, and non-significant main effect of block $F(4, 26) = 1.41, p = .233$, and group, $F(1, 26) = 2.40, p = .133$. The interaction occurred because the control group improved over blocks whereas the olanzapine group did not show a significant change in correct responses over blocks, as shown in Sections 4.1.3 and 4.1.4.

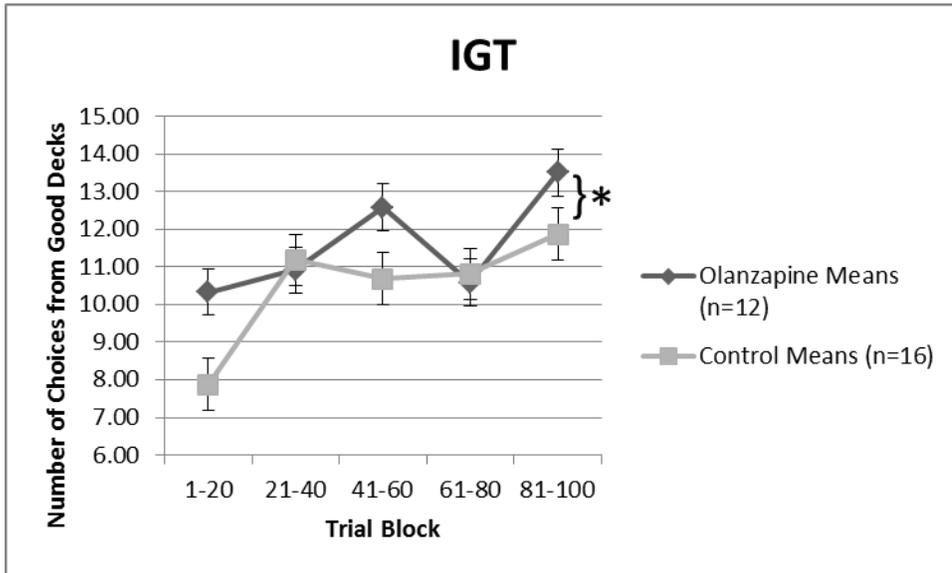
For the IGT, the control group learned. The olanzapine group also appeared to learn but their performance decreased from block 41-60 to block 61-80 (Fig. 6). ANOVA revealed only a significant main effect of block $F(4, 26) = 4.28, p = .003$; the group effect, $F(1, 26) = 1.57, p = .221$, and interaction, $F(4, 26) = .988, p = .418$, were non-significant.

Figure 5: Performance on the Probabilistic Classification Learning (PCL) Task



*Asterisk indicates a significant block effect for the control group by analysis of simple effects of blocks for each group following a significant blocks by group interaction in analysis of variance.

Figure 6: Performance on the Iowa Gambling Task (IGT)



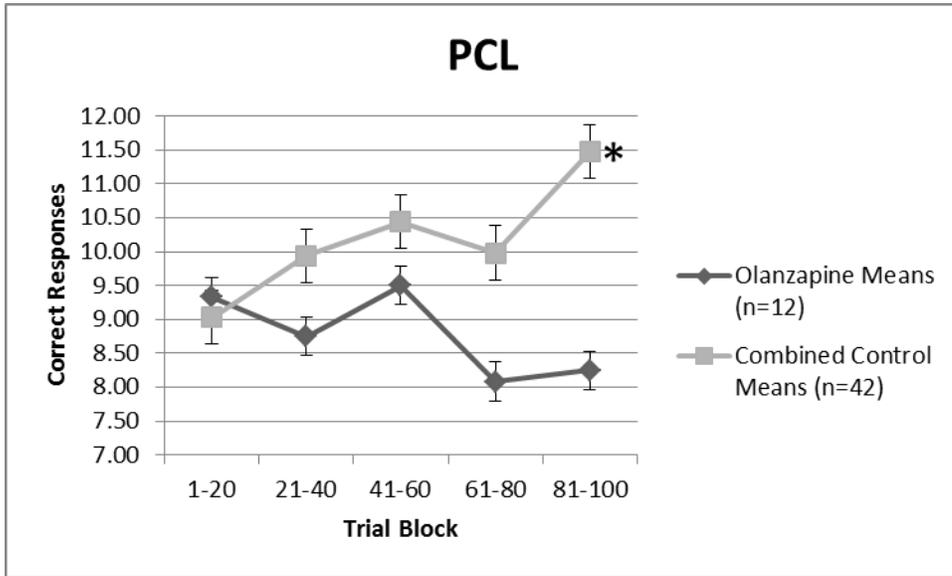
*Asterisk indicates a significant block effect in a group by blocks analysis of variance.

4.2.2 Combined Students and Controls compared with Olanzapine

The student and control groups combined learned both the PCL and the IGT and ANOVA failed to reveal significant main effect of group or group by block interactions; therefore, the two groups combined were compared to the olanzapine group. On the PCL, the combined student and control group learned whereas the olanzapine group showed no improvement over blocks (Fig. 7). ANOVA revealed a significant main effect of group, $F(1, 52) = 5.35, p = .025$, and a significant interaction $F(4, 52) = 2.64, p = .035$, with a non-significant main effect of block, $F(4, 52) = 1.11, p = .351$. The interaction confirmed that the combined group but not the olanzapine group learned the PCL task.

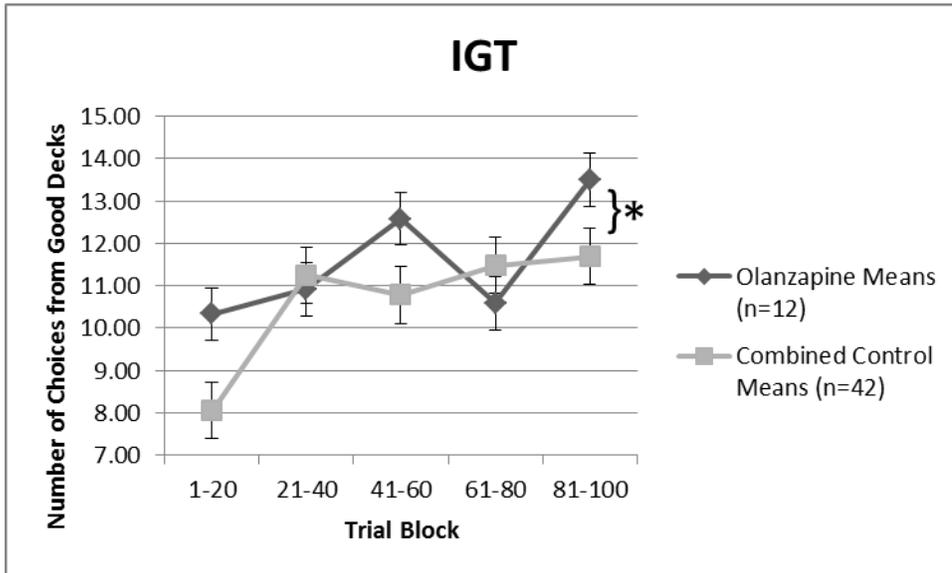
For the IGT both groups appeared to learn (Fig. 8). This was supported by a significant main effect of block, $F(4, 52) = 4.77, p < .001$, with the group effect, $F(1, 52) = .891, p = .350$, and interaction, $F(4, 52) = 1.74, p = .142$, being non-significant.

Figure 7: Performance on the Probabilistic Classification Learning (PCL) Task



*Asterisk indicates a significant block effect for the control group by analysis of simple effects of blocks for each group following a significant blocks by group interaction in analysis of variance.

Figure 8: Performance on the Iowa Gambling Task (IGT)



*Asterisk indicates a significant block effect in a group by blocks analysis of variance.

4.2.3 Deck Choice on the IGT

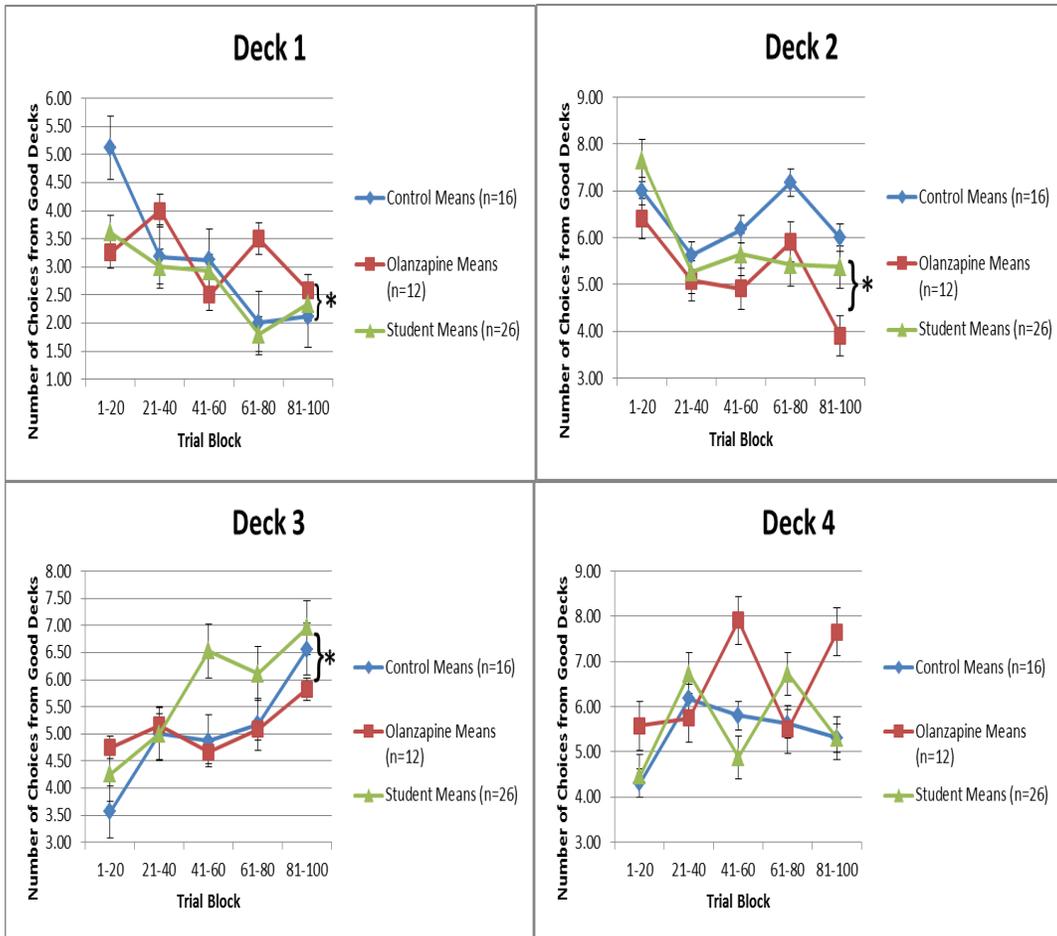
Learning over trials on the IGT is defined by a shift away from the bad decks (decks 1 and 2) and moving toward selection from the good decks (decks 3 and 4). ANOVA were carried out to compare number of choices from each deck across trial blocks for the combined student and control group, and the olanzapine group. For deck 1, the student and control groups chose less over blocks; although the olanzapine group tended towards choosing less from bad deck 1 over trial blocks, its performance over blocks was more variable (Fig. 9, Deck 1). The overall shift away from the bad decks was revealed as a significant block effect, $F(4, 52) = 3.75, p = .006$ in the ANOVA and the variable block-to-block performance of the olanzapine group was revealed in the significant interaction, $F(4, 52) = 3.12, p = .016$; the group effect was not significant, $F(1, 52) = .557, p = .459$.

Groups tended to choose less from bad deck 2 over trial blocks although this tendency was weak in the control group (Fig. 9, Deck 2). ANOVA revealed only a significant block effect, $F(4, 52) = 3.03, p = .018$, with a non-significant group effect, $F(1, 52) = 1.50, p = .226$, and interaction, $F(4, 52) = .342, p = .850$.

Groups chose more from good deck 3 over trial blocks (Fig. 9, Deck 3). ANOVA revealed no significant effects although the block effect approached significance, $F(4, 52) = 2.24, p = .066$; group effect, $F(1, 52) = .262, p = .611$, interaction, $F(4, 52) = .788, p = .534$.

On good deck 4, although block-to-block performance was quite variable for the student and olanzapine groups, there was a mild trend towards increased choices from this deck over trial blocks (Fig. 9, Deck 4). The trial-blocks effect in ANOVA was not significant, $F(4, 52) = 1.39$, $p = .238$, and neither was the group effect, $F(1, 52) = 1.18$, $p < .281$; the interaction approached significance, $F(4, 52) = 2.39$, $p = .052$, reflecting the variability in block-to-block performance.

Figure 9: Number of choices from the bad decks (Deck 1 and 2) and from the good decks (Deck 3 and 4) over trials



*Asterisk indicates a significant block effect in a group by blocks analysis of variance.

4.2.4 Additional Atypical Medication Groups

Participants included patients treated with aripiprazole ($n = 2$), risperidone ($n = 2$), aripiprazole plus risperidone ($n = 1$) or olanzapine plus risperidone ($n = 2$). Due to insufficient sample sizes an ANOVA could not be conducted. Preliminary data (Figures 10 and 11) suggest that those taking risperidone did not learn either task. Those taking aripiprazole may have learned the PCL but not the IGT. For the few patients treated with more than one SGA, there was little evidence of learning on either task.

Figure 10: Performance of patients treated with risperidone, aripiprazole, olanzapine plus risperidone (Ola/Ris) or risperidone plus aripiprazole (Ris/Ari) and controls on the PCL

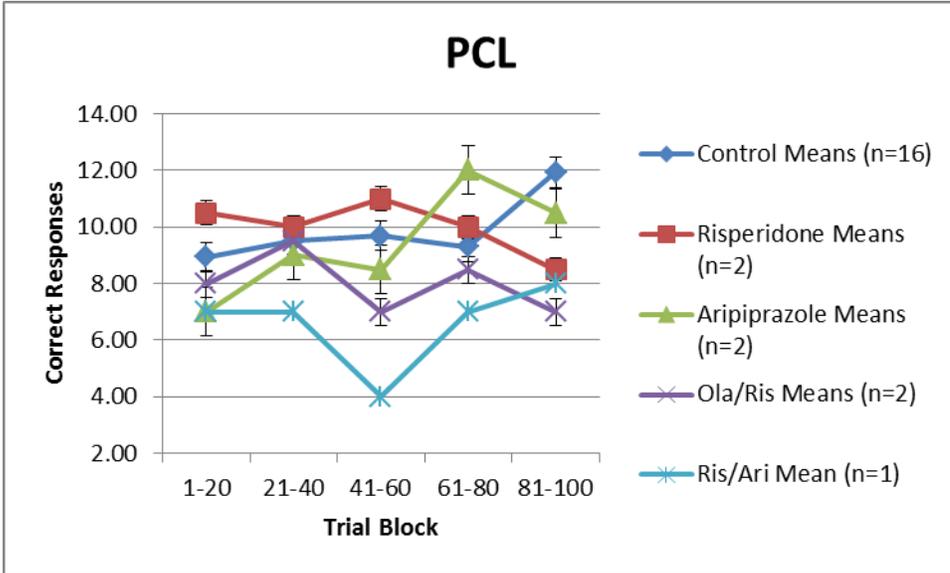
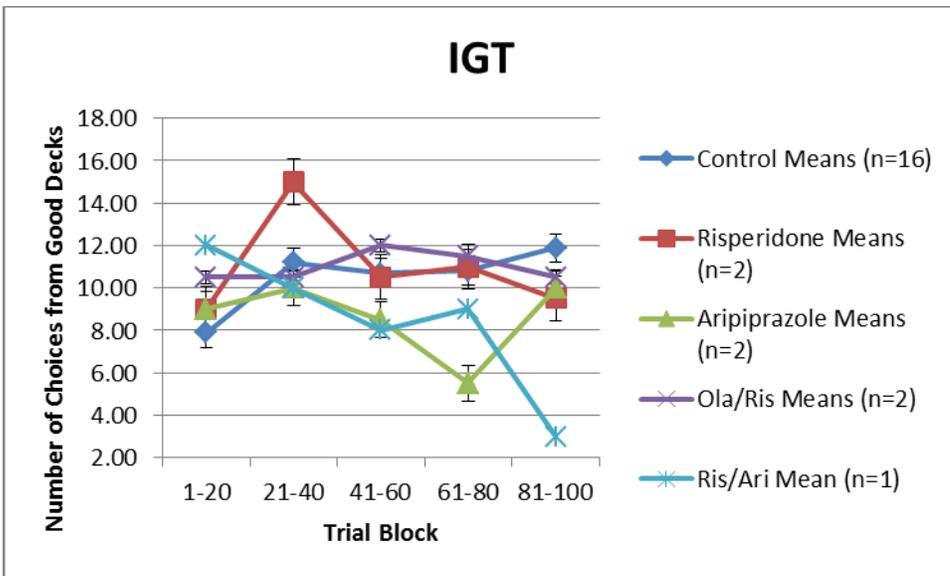


Figure 11: Performance of patients treated with risperidone, aripiprazole, olanzapine plus risperidone (Ola/Ris) or risperidone plus aripiprazole (Ris/Ari) and controls on the IGT



Chapter 5

Discussion

5.1 General Findings

The pilot study with students showed a significant block effect reflecting learning in both the PCL ($p = .016$) and IGT ($p = .002$). Although normal learning occurred in the IGT with the control group ($p = .040$), their performance on the PCL only approached significance ($p = .077$). However, following ANOVA with student and control groups, no significant effects were detected for groups or group by block interactions. This suggests comparable performances on both tasks, although it appears that learning was reached later with controls on the PCL (in the final trial block). This statistical evidence supported the combining of the student and control groups despite differences in demographic variables.

On the PCL the olanzapine group was impaired as reported previously using the same task (Wasserman et al. 2012). On the IGT the olanzapine group performed like controls in contrast to a previous report that the olanzapine group did not learn over trials on the IGT (Wasserman et al., 2012). The reasons for different performance on the IGT for the olanzapine groups in the present study versus that in the Wasserman et al. (2012) study are unclear. However, the present group size was small ($n = 12$) whereas Wasserman et al. (2012) had 21 participants in the olanzapine group who were matched for sex and age, but not education with controls. It will be important to add participants to the present group before any further conclusions are made.

SGAs are probably not a homogeneous group of compounds. For example, clozapine has a localized effect of increasing Fos expression (a marker of neuronal activity) in the infralimbic and medial areas of the PFC (Deutch, & Duman, 1996). Unlike clozapine, other SGAs including olanzapine, risperidone, remoxipride, and melperone, increase Fos expression in the medial, but not dorsolateral, area of the striatum (Beninger, Baker, Florczynski, & Banasikowski, 2010). However, it is of particular interest that olanzapine appears to be rather non-localized in its effects, in so far as the association to task impairments that rely on disparate brain areas is maintained.

Immunoblot studies with rats using antagonist pretreatments for both D1-like, and D2-like, receptors failed to attenuate Fos protein expression in the PFC when using clozapine (Deutch, & Duman, 1996). Although all antipsychotics have an effect of increasing Fos expression in the shell of the nucleus accumbens, action on a non-DA receptor may help to explain some of the impairments seen in olanzapine, in addition to clozapine, with tasks dependent on intact PFC functioning (Deutch, & Duman, 1996). Further complicating the differences between antipsychotics is research with first-episode schizophrenia spectrum disorders. In an open-label, randomized, study CrespoFacorro et al. (2009) looked for significant differences between patients taking haloperidol, olanzapine, or risperidone at baseline, six-months, and one year testing with a neuropsychological battery consisting of nine cognitive domains. At one year follow up all antipsychotic medications were equally effective in attenuating cognitive deficits in participants (CrespoFacorro et al., 2009).

The olanzapine group failed to show learning over blocks on the PCL compared with the control group, yet this difference was only statistically significant ($p = .025$) when the control and student groups were combined. On the IGT the olanzapine group had a comparable, yet more variable, performance to the combined student and control group supported by a significant main effect of block ($p = .001$). This variability, compared with student and control groups, was particularly apparent on deck one when observing choices from bad decks across trial blocks, suggesting that patients were not as keen as healthy controls in deciphering penalties associated with high risk choices.

As expected, significant differences were found between the control group and the olanzapine group on both the MMSE and BPRS with the patient group having a poorer outcome. Despite an effort to match participants on demographic information, significant differences in age ($p = .001$), education ($p = .037$), and gender ($p = .019$) were found between the olanzapine and control groups. Any impairment found in this study could be the result of schizophrenia, anti-psychotic type, or the specific dosage of their medication.

Assignment to groups was not random as patients were already receiving treatment for at least four weeks prior to inclusion in the study. Therefore, there is no way to remove a prescribing bias amongst psychiatrists that may have selected individuals for their treatment based on either resistance to other medications or symptomatology. It is also possible that any deficits observed in patients may be due to the use of prior anti-psychotic medications, or psychoactive substances. It is noteworthy that despite these

limitations in previous studies e.g., Beninger et al., 2003, Wasserman et al., 2012, predicted group differences in performance on the PCL and IGT were found.

Furthermore, it was found that groups treated with some medications, e.g., typical antipsychotics or risperidone, were more impaired on the PCL than the IGT whereas groups treated with other medications, e.g., an atypicals group that included participants treated with one of several different SGAs or a group treated with clozapine, were more impaired on the IGT than the PCL. This dissociation lessens concerns that effects can be attributed to a putative prescribing bias or specific features of the illness.

5.1.1 Additional Atypical Medication Groups

One of the aims of the current study was to investigate the effects of aripiprazole on non-declarative memory performance when compared with risperidone, olanzapine, and controls. Although numbers were small and data have to be viewed with caution, aripiprazole-treated patients may have learned the PCL but not the IGT; those treated with risperidone showed little evidence of learning either task. Previous research has shown that patients with schizophrenia treated with SGAs that affect the VMPFC, but not the dorsal striatum, are impaired on the IGT, but not the PCL, while those taking FGAs (or risperidone) that affect the dorsal striatum, but not the VMPFC, have the inverse result (Beninger et al., 2003; Wasserman et al., 2012). The observation that the aripiprazole group may have shown learning on the PCL, but not the IGT, is interesting in this regard. The effect of aripiprazole treatment on learning in these two tasks has

never been studied, and although caution must be taken in interpretation, these preliminary data suggest a possible impairment of the IGT but not the PCL. This would be contrary to our hypothesis that aripiprazole would have an effect more like risperidone or FGA medications.

Preliminary data suggest the olanzapine plus risperidone group failed to learn the PCL or IGT. In previous research people with schizophrenia taking risperidone were impaired on the PCL but not the IGT so it would be interesting to investigate whether or not an olanzapine plus risperidone treatment group would fit this model. More participants are needed in the olanzapine plus risperidone, risperidone plus aripiprazole groups.

5.2 Future Studies

Future studies should investigate several areas for a more advanced understanding of the effect of anti-psychotic medications on memory performance. Prior research has shown that antipsychotic medications can impair verbal learning and recognition memory, semantic fluency, and executive planning functions (Jamrozinski, Gruber, Kemmer, Falkai, & Scherk, 2009). As dosages vary from participant to participant replication of these results or findings from similar studies should seek a controlled dosage so as to minimize variability due to drug exposure. All participating patients in this study had been on their respective medication for at least four weeks prior to inclusion in the study and were asked to be free from other psychoactive drugs up to 24 hours prior to testing.

Secondly, although this study focused on people with schizophrenia a more holistic approach to disorders that both FGA and SGA medications treat would help account for the effects of these medications on memory in a broader way. Because individuals were assigned to groups based on medication they were already taking this was a quasi-experiment. If feasible, the goal of future research should be to randomize participants to groups prior to treatment. Beyond this, a pre- and post-test either with regard to new medication or drug-naïve patients would help strengthen the interpretation of results in this type of study.

Lastly, the nature of these two tasks is to assess NDM; however, only one of the tasks, the IGT, provides cumulative feedback with regard to total correct. The differential sensitivity of each task toward striatal or VMPFC damage has been established in the literature. However, adapting each of the tasks toward or away from processes that require executive functioning e.g., ongoing cumulative feedback, may be an advantageous way of defining the components of each task that lead to the kind of variance displayed in patients being treated with different medications (Beninger et al., 2003).

Chapter 6

Summary and Conclusions

The objective of the present study was to gain further insight into possible cognitive changes in patients with schizophrenia treated with olanzapine. The experiments carried out sought to further elaborate on the contributions to dissociating cognitive changes associated with schizophrenia from those associated with the medications used to treat schizophrenia. Preliminary data on aripiprazole are promising and need to be followed up with larger sample sizes. Although this study only included those afflicted with schizophrenia the larger goal of these experiments is to detail the effects of anti-psychotic medications that have action in disparate areas of the brain so as to better understand and improve upon treatments for mental illness. Considering the host of disorders treated with anti-psychotics, e.g., bipolar disorder, obsessive compulsive disorder, generalized anxiety disorder, treatment resistant depression, developmental disabilities and other mental illnesses, it is worthwhile to investigate just how these medications affect the brain, and specifically memory (Haw & Stubbs, 2007; Jamrozinski et al., 2009). Memory is an integral part of most conscious and unconscious behaviours and the impairments so far observed in experiments delineate the necessity for research into describing and improving upon the conditions experienced by those who require anti-psychotic medications. There is ample evidence suggesting that learning impairments follow use of anti-psychotic medication and are likely caused if not

exacerbated by their use in some cases (Harris et al., 2009). Research into understanding the etiology of schizophrenia and the medications used to treat it, alongside related disorders, is concordant with advancing an understanding of the brain itself.

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