ANTIPSYCHOTIC MEDICATIONS:
LINKING RECEPTOR ANTAGONIST PROPERTIES
TO NEUROPSYCHOLOGICAL FUNCTIONING

by

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Abstract

Antipsychotic medications are thought to contribute to the neuropsychological impairments associated with schizophrenia, but specific links with pharmacology are not well established. This study investigated associations of specific medication properties with neuropsychological and psychiatric symptoms in a first-episode psychosis sample. Medication doses and indices of receptor antagonism were used to estimate dopamine antagonist, serotonergic antagonist, and anticholinergic loads (i.e., impact of participants' medications on those receptors). Results indicated that higher anticholinergic load was associated with poorer verbal long-term memory and higher D_2 load was associated with poorer motor functioning. Additional exploratory analyses indicated that in non-smokers, higher D_1 load was associated with more severe negative symptoms, whereas higher 5-HT_{2A} load was associated with less severe negative symptoms. Furthermore, in smokers, higher 5-HT_{2A} load was associated with poorer verbal working memory. These results support the validity of estimating medication receptor loads to elucidate specific and dissociable effects of antipsychotic medication properties.

Keywords: psychosis; cognition; anticholinergic; dopamine; serotonin; negative symptoms

For Chris

Acknowledgments

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**Antipsychotic Medications: Linking Receptor Antagonist Properties
to Neuropsychological Functioning**

Psychosis is a core feature of schizophrenia spectrum disorders, and can occur in

other disorders including bipolar disorder and major depressive disorder. Patients

presenting with a first episode of psychosis may recover, but many remain chronically ill,

suffering from a range of psychotic, affective and cognitive symptoms. The symptoms of

schizophrenia are traditionally divided into positive symptoms including hallucinations,

delusions, and disorganized thinking, and negative symptoms including avolition,

anhedonia, alogia, and affective flattening (Andreasen & Olsen, 1982; Crow, 1985).

Positive symptoms can be subdivided into psychotic and disorganized symptoms

(Andreasen, Arndt, Alliger, Miller, & Flaum, 1995). Negative symptoms can be

subdivided into primary and secondary symptoms; primary negative symptoms are direct

effects of the illness, whereas secondary negative symptoms are indirectly caused by

factors such as depression, medication side effects, self-protective reduction of

stimulation, and absence of social stimulation (Carpenter, Heinrichs, & Wagman, 1988).

Cognitive symptoms include a wide range of deficits (Albus et al., 2006; Bilder et al.,

2000; Heinrichs & Zakzanis, 1998) that are evident at the first episode of psychosis

(Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Some of the most well

established deficits are in the areas of verbal learning and memory and executive

functioning (Albus et al., 2006; Heinrichs & Zakzanis, 1998).

Antipsychotic medications alleviate the positive symptoms of psychosis, and some of

the newer atypical antipsychotics are modestly effective in alleviating negative symptoms

(see Leucht et al., 2009), although the medication properties responsible for negative

symptom efficacy are not well understood (Erhart, Marder, & Carpenter, 2006).

However, some of the medications that improve positive and negative symptoms may

worsen cognition, including that associated with the operations of the prefrontal cortex

(Castner, Williams, & Goldman-Rakic, 2000; Goldberg et al., 1993; McGurk et al., 2004;

Meltzer & McGurk, 1999; Minzenberg, Poole, Benton, & Vinogradov, 2004; Reilly,

Harris, Keshavan, & Sweeney, 2006; Reilly, Harris, Khine, Keshavan, & Sweeney, 2007;

Strauss, Reynolds, Jayaram, & Tune, 1990). Understanding the factors, including

medication factors, that influence negative symptoms and cognitive impairments in early

psychosis is of utmost importance. Indeed, negative symptoms and cognitive abilities are

strong predictors of social and occupational functioning in patients with schizophrenia

(Bilder et al., 2000; Green, 1996; Meltzer, Thompson, Lee, & Ranjan, 1996; Milev, Ho,

Arndt, & Andreasen, 2005; Velligan & Bow-Thomas, 1999; Velligan et al., 1997).

In particular, the pharmacological profile of a given antipsychotic medication may

determine its impact on cognition and negative symptoms. All antipsychotic medications

share the property of blocking D_2-type dopamine receptors (Kapur & Seeman, 2001), and

select compounds also block muscarinic cholinergic receptors, D_1-type dopamine

receptors, and serotonin type 2A ($5-HT_{2A}$) receptors (Richelson & Souder, 2000). Table 1

illustrates the blockade[1] of several common antipsychotic compounds on these receptors.

Previous research has demonstrated that the anticholinergic potency of antipsychotic

medications may indeed influence cognition in psychosis. Minzenberg and colleagues

(2004) developed a pharmacological index of the relative anticholinergic potencies of

psychiatric medications based on published reports of in vitro brain muscarinic receptor

antagonism. Higher anticholinergic load as estimated by this index predicted poorer

declarative memory functioning[2] in a chronic schizophrenia spectrum disorder sample

(Minzenberg et al., 2004).

Table 1. Binding Affinities (K_i) for Serotonergic, Muscarinic Cholinergic, and Dopaminergic Receptors.

Medication	Serotonergic (5-HT$_{2A}$)	Muscarinic	Dopaminergic (D$_1$)	Dopaminergic (D$_2$)
Clozapine	++++	+++	++	+++
Risperidone	+++++	+-	+++	+++++
Olanzapine	++++	+++	+++	+++
Quetiapine	++	+	++	+++
Haloperidol	+++	+-	+++	+++++
Loxapine	++++	++	+++	++++

Note. K_i (nM) 10 000 – 100 000 = +-; 1000 – 10 000 = +; 100 – 1000 = ++; 10 – 100 = +++;

1 – 10 = ++++; 0.1 – 1 = +++++

Objective

The current research aimed to replicate Minzenberg and colleagues' (2004) findings

in a first-episode psychosis (FEP) sample, drawing from and extending their methods to

investigate the role of other antipsychotic medication properties in modifying

neuropsychological functions and psychiatric symptoms. Specifically, the current study

examines the effects of dopaminergic, serotonergic, and muscarinic antagonism from

medications on specific neuropsychological functions and psychiatric symptoms.

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[1] Represented by equilibrium dissociation constant (K_i) values.

[2] In this study, anticholinergic load was associated with a declarative memory factor derived by principle component analysis, but was not associated with factors representing general intelligence/attention, visual attention, or "other" cognition.

Previous studies using randomized controlled trial designs have produced a wealth of knowledge about the effects of various antipsychotic medications. However, results are not always consistent and the overall pattern is difficult to interpret due to three issues. First, in comparisons across medications, it is difficult to determine which medication properties may be the cause of any differences in neuropsychological functioning. Second, it is difficult to account for adjunctive medications, such as anticholinergics, that may affect neuropsychological functioning. Third, apparent medication effects may in fact be accounted for by practice effects in studies that do not include control groups (e.g., Galletly, Clark, McFarlane, & Weber, 1997; Goldberg et al., 1993; Hoff et al., 1996; Rossi et al., 1997; Stip & Lussier, 1996; Zahn, Pickar, & Haier, 1994).

Following the technique developed by Minzenberg and colleagues (2004), the current study was designed to evaluate the utility of dopaminergic, serotonergic, and cholinergic impact scales that are independent of medication type. These scales may be valuable in providing results that complement findings derived from overall comparisons across medications. In particular, the current method enables analysis across multiple medications and can thus produce results that are applicable to understanding the impact of diverse medication regimens, including polypharmacy.

This line of research stands to benefit neuropsychologists by providing more precise knowledge of specific medication influences on neuropsychological test performance. Furthermore, by gaining more detailed information about the potential impact of specific medication regimens on cognitive and negative symptoms, other health care professionals may be better equipped to mitigate adverse medication effects.

Medication impacts on dopaminergic, serotonergic, and cholinergic receptors were predicted to have specific and dissociable effects. Previous findings suggesting links

between these receptors and neuropsychological functioning or psychiatric symptoms are outlined below.

Dopamine Receptors

Subcortical dopamine and D_2 receptors. The dopamine model of neuropathology in schizophrenia suggests that excessive dopamine in subcortical areas, where D_2 receptors are predominantly found (Camus, Javoy-Agid, Dubois, & Scatton, 1986), underlies positive symptoms of the illness (Abi-Dargham, 2004; Davis, Kahn, Ko, & Davidson, 1991). Consistent with this model, the dopamine agonist amphetamine exacerbates the positive symptoms of schizophrenia (Angrist, Rotrosen, & Gershon, 1980).

Antipsychotic medication blockade of dopamine D_2 receptors alleviates the positive symptoms of schizophrenia, but also negatively impacts motor functioning (Farde et al., 1992; Scherer et al., 1994) and can induce extrapyramidal side effects. This is particularly true for typical antipsychotic medications, which are defined by high D_2 antagonism and low serotonin antagonism (Meltzer, Matsubara, & Lee, 1989). In contrast, atypical antipsychotics are effective at doses that generally do not cause extrapyramidal side effects (Bezchlibnyk-Butler, Jeffries, & Virani, 2007; Meltzer et al., 1989). Indeed, research suggests that patients taking typical antipsychotics show high striatal D_2 receptor occupancy and are more likely to suffer from extrapyramidal side effects, whereas patients taking the atypical medication clozapine show lower striatal D_2 receptor occupancy and are less likely to suffer from extrapyramidal side effects (Farde et al., 1992). In terms of neuropsychological functions, a strong linear relationship has been demonstrated between higher D_2 receptor occupancy and poorer fine motor ability as measured by reduction of handwriting area, in patients taking antipsychotic medications

(Kuenstler, Juhnhold, Knapp, & Gertz, 1999). Higher striatal D_2 receptor availability is also strongly associated with better fine motor speed (Yang et al., 2004).

Cortical dopamine and D_1 receptors. The dopamine model of neuropathology in schizophrenia also suggests that insufficient dopamine in the cortex, where D_1 receptors are much more prevalent than D_2 receptors (Goldman-Rakic, Lidow, & Gallager, 1990; Hall et al., 1994), underlies negative and cognitive symptoms of the disorder (Abi-Dargham, 2004; Davis et al., 1991). Consistent with this model, the dopamine agonist amphetamine can improve set shifting performance in schizophrenia patients (Daniel et al., 1991) and patients with schizotypal personality disorder (Kirrane et al., 2000). Moreover, amphetamine and other non-specific dopamine agonists have been shown to improve negative symptoms (Bodkin et al., 1996; Gerlach & Lühdorf, 1975; Levi-Minzi, Bermanzohn, & Siris, 1991; van Kammen & Boronow, 1988; but see also Angrist, Peselow, Rubinstein, Corwin, & Rotrosen, 1982).

Specific D_1 agonists have been tested in monkeys, and were found to improve working memory in aged monkeys, who have naturally low levels of dopamine, but not in young monkeys with normal dopamine levels (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Castner & Goldman-Rakic, 2004). Furthermore, the D_1 agonist ABT-431 reverses working memory deficits associated with chronic antipsychotic drug therapy (Castner et al., 2000). Conversely, the D_1 antagonist SCH-223390 impairs spatial working memory in young monkeys (Arnsten et al., 1994).

Researchers have investigated several D_1 antagonists as potential antipsychotics in small samples, but have not found any reliable alleviation of psychosis (de Beaurepaire, Labelle, Naber, Jones, & Barnes, 1995; Den Boer et al., 1995; Karle et al., 1995; Karlsson et al., 1995). However, the results of two of these studies (Den Boer et al., 1995;

Karle et al., 1995) showed a possible reduction of negative symptoms, in contrast to the worsening of negative symptoms that might be expected based the attribution of negative symptoms to a lack of cortical dopamine. Further studies in humans have not been conducted, as the D_1 antagonists were associated with poor adherence and a variety of adverse events. It therefore remains unclear whether the observed improvements in negative symptoms are robust.

Further support for a link between cortical dopamine and cognitive symptoms comes from PET studies investigating the availability of prefrontal D_1 receptors in schizophrenia. Early studies using the ligand C-Labeled SCH-23390 produced inconsistent results, indicating that schizophrenia patients had low (Okubo et al., 1997) or normal (Karlsson, Farde, Halldin, & Sedvall, 2002) D_1 binding, and that low binding was associated with poorer cognition and more severe (Okubo et al., 1997) or less severe (Karlsson et al., 2002) negative symptoms. However, a more recent study using the newer and more specific ligand $[^{11}C]$NNC 112 demonstrated high binding to D_1 receptors in the prefrontal cortex, perhaps reflecting a compensatory mechanism in response to low cortical dopamine in schizophrenia (Abi-Dargham, 2003). Consistent with this compensatory interpretation, higher availability of prefrontal D_1 receptors in schizophrenia patients was associated with poorer working memory performance (Abi-Dargham, 2003). D_1 binding was not associated with negative symptoms in this study. Thus, if poor cognition is associated with compensatory up-regulation of D_1 receptors due to low cortical dopamine in schizophrenia, D_1 antagonism would be expected to cause further impairments in cognition, while D_1 agonism would be expected to improve cognition. Accordingly, D_1 agonists are currently being investigated as cognition-

enhancing drugs for schizophrenia (Buchanan, Freedman, Javitt, Abi-Dargham, & Lieberman, 2007; Galletly, 2009; George et al, 2007).

5-HT$_{2A}$ Receptors

Antipsychotic medications with 5-HT$_{2A}$ antagonist properties may improve both cognition and negative symptoms by increasing prefrontal dopamine release. Although studies of animals and healthy humans have demonstrated that 5-HT$_{2A}$ agonism can improve cognition while 5-HT$_{2A}$ antagonism can impair cognition, these observations do not account for the effect of combined D$_2$ and 5-HT$_{2A}$ blockade in antipsychotic medications. Indeed, the 5-HT$_{2A}$ blockade commonly found in atypical antipsychotics results in increased prefrontal dopamine release (Alex & Pehek, 2007; Elsworth, Jentsch, Morrow, Redmond, & Roth, 2008; Kuroki, Meltzer, & Ichikawa, 1999; Horacek et al., 2006; Kapur & Remington, 1996; Moghaddam & Bunney, 1990; Nomikos, Iurlo, Andersson, Kimura, & Svensson, 1994; Pehek & Yamamoto, 1994; Volonte, Monferini, Cerutti, Fodritto, & Borsini, 1997).

5-HT$_{2A}$ receptors and cognition. The direct impact of 5-HT$_{2A}$ antagonism on cognition in medicated schizophrenia patients has been demonstrated in one study. Poyurovsky and colleagues (2003) found that the 5-HT$_{2A}$ antagonist mianserin improved spatial working memory in medicated patients with schizophrenia. Verbal working memory may also benefit from the combination of 5-HT$_{2A}$ antagonism and D$_2$ antagonism, although this has not been directly investigated.

5-HT$_{2A}$ receptors and negative symptoms. Several studies of medicated schizophrenia patients suggest that the increased cortical dopamine release induced by combined 5-HT$_{2A}$ and D$_2$ antagonism may improve negative symptoms (see Horacek et

al., 2006). In particular, administering the 5-HT$_{2A}$ antagonists mianserin or ritanserin to medicated schizophrenia patients reduces negative symptoms (Gelders, 1989; Hayashi et al., 1997; Mizuki, Kajimura, Imai, & Suetsugi, 1990; Mizuki et al., 1992; Reyntjens, Gelders, Hoppenbrouwers, & Vanden Bussche, 1986; but see also Shiloh et al., 2002).

Comparisons of negative symptom efficacy between typical and atypical medications support the contention that combined 5-HT$_{2A}$ and D$_2$ antagonism may improve negative symptoms. Atypical antipsychotics occupy both 5-HT$_{2A}$ and D$_2$ receptors, and this combination of blockade may underlie the superiority of atypical relative to typical antipsychotics in alleviating the negative symptoms of schizophrenia (Carman, Peuskens, & Vangeneugden, 1995; Davis & Chen, 2002; Leucht et al., 2009; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999; Marder & Meibach 1994; Moller, 2003; Wahlbeck, Cheine, Essali, & Adams, 1999; but see also Buckley & Stahl, 2007; meta-analytic effect sizes are listed in Table A1), as typical antipsychotics primarily occupy D$_2$ receptors.

Muscarinic Cholinergic Receptors

Muscarinic cholinergic antagonism helps to prevent motor side effects of antipsychotic medications (Arana, Goff, Baldessarini, & Keepers, 1988), but also causes deficits in long-term memory[3] (LTM; Gold, 2003; Power, Vazdarjanova, & McGaugh, 2003; Thiel, 2003). The muscarinic cholinergic antagonist scopolamine impairs verbal LTM in healthy participants (Ebert, Oertel, Wesnes, & Kirch, 1998; Ghoneim & Mewaldt, 1975). Similarly, in medicated patients with schizophrenia, the use of adjunctive anticholinergic medications (Brebion, Bressan, Amador, Malaspina, &

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[3] That is, the relatively permanent store of information that is no longer maintained in short-term or working memory after a delay or distraction (Atkinson & Shiffrin, 1968; Butters & Delis, 1995).

Gorman, 2004; Sweeney, Keilp, Haas, Hill, & Weiden, 1991) and high serum anticholinergic levels are associated with deficits in LTM (Perlick, Stastny, & Katz, 1986; Strauss et al.,1990; Tracy, Monaco, Giovannetti, Abraham, & Josiassen, 2001; Tune, Strauss, Lew, Breitlinger, & Coyle, 1982). As previously reported, Minzenberg and colleagues (2004) found that increased anticholinergic load estimated on the basis of one or more antipsychotic medications predicted impairment in verbal learning and memory in a chronic schizophrenia spectrum disorder sample. This finding has not yet been replicated, although a quantitative review of antipsychotic effects on LTM has supported a relationship between the anticholinergic properties of different types of medications and their impacts on LTM (Thornton, Van Snellenberg, Sepehry, & Honer, 2006). New pharmacological treatments that stimulate cholinergic functioning are currently being investigated for the treatment of cognitive deficits in schizophrenia (Galletly, 2009).

Hypotheses

The above evidence suggests that the impacts of antipsychotic medications on neuropsychological functioning and psychiatric symptoms are related to their particular pharmacological properties in predictable ways. In this study of FEP patients, it was hypothesized that:

1. Higher estimated muscarinic cholinergic antagonism from psychiatric medications would be associated with poorer verbal LTM,[4] but would not be associated with motor functioning, working memory, or negative symptoms.

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[4] Minzenberg et al., 2004; Thornton et al., 2006

2. Higher estimated dopamine D_2 antagonism from psychiatric medications would be associated with poorer motor functioning,[5] but would not be associated with verbal LTM, working memory, or negative symptoms.

3. Higher estimated D_1 antagonism from psychiatric medications would be associated with poorer working memory and more severe negative symptoms,[6] but would not be associated with verbal LTM or motor functioning.

4. Higher $5\text{-}HT_{2A}$ antagonism from psychiatric medications in the context of D_2 antagonism would be associated with better working memory[7] and less severe negative symptoms,[8] but would not be associated with verbal LTM or motor functioning.

Table 2 illustrates these hypotheses.

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[5] Farde et al., 1992; Kuenstler et al., 1999; Scherer et al., 1994; Yang et al., 2004

[6] Abi-Dargham, 2003; Arnsten et al., 1994

[7] Poyurovsky et al., 2003

[8] Gelders, 1989; Hayashi et al., 1997; Horacek et al., 2006; Mizuki et al., 1990; Mizuki et al., 1992; Reyntjens et al., 1986

Table 2. Hypothesized Associations

Hypothesis	Neuropsychological Functions and Psychiatric Symptoms			
	Verbal Long-term Memory	Motor Functioning	Working Memory	Negative Symptoms
1. Higher cholinergic antagonism	**Poorer**	Unrelated	Unrelated	Unrelated
2. Higher D_2 antagonism	Unrelated	**Poorer**	Unrelated	Unrelated
3. Higher D_1 antagonism	Unrelated	Unrelated	**Poorer**	**More Severe**
4. Higher 5-HT$_{2A}$ antagonism	Unrelated	Unrelated	**Better**	**Less Severe**

Method

Participants and Procedures

The current study used data collected as part of the 2002 - 2007 "Interactions of Development, Early Life Experience and Genetic Predisposition in Schizophrenia" study.[9, 10] Inclusion criteria were FEP, fluency in English,[11] and no antipsychotic treatment or stable antipsychotic treatment for at least 3 weeks prior to the assessment. Forty-five males and 23 females aged 15 to 50 completed the assessments and met the inclusion criteria.[12] Thirty-two participants (47.1%) were smokers. Premorbid intellectual functioning was estimated with the North American Adult Reading Test (NAART; Blair & Spreen, 1989). Demographics, symptoms, diagnoses, and medications are listed in Table 3.

Using $\alpha = .05$, with three predictors in the model, power tables (Cohen, Cohen, West, & Aiken, 2003) indicate that a sample of 69 participants will result in power of 0.80 for

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[9] Primary Investigator: W.G. Honer, MD, LMCC, FRCPC, Professor, Medicine/Psychiatry, University of British Columbia. Co-Investigators: A. Phillips, PhD, RPsych, Professor, Medicine/Psychiatry, University of British Columbia; A. Thornton, PhD, RPsych, Associate Professor, Psychology, Simon Fraser University; J. Kennedy, MD, FRCPC, Professor, Centre for Addiction and Mental Health, University of Toronto; A. El Husseini, PhD, Assistant Professor, Medicine/Psychiatry, University of British Columbia; A. MacKay, MD, Professor, Medicine/Radiology & Science/Physics and Astronomy, University of British Columbia.

[10] All participants were recruited through the Early Psychosis Identification and Intervention (EPII) program in British Columbia.

[11] Participants were deemed fluent in English if they were born in an English-speaking country (Canada, US, UK, or Australia) or had lived in an English-speaking country since before starting high school.

[12] Of 84 potential participants, eight were excluded for unclear or recently changed antipsychotic medications or poor medication adherence, one was excluded for lack of engagement during testing, two were excluded for diagnosis of substance-induced psychosis, and four were excluded for non-fluency in English. One additional participant, who had the most severe psychiatric symptoms by a margin of 16 points on the PANSS, emerged as a multivariate outlier and was excluded.

the detection of an $R^2 = 0.14$. This corresponds to detection of an effect that is conventionally defined as medium to large (Cohen, 1992).

 The study procedures are detailed in Appendix B. The protocol for the original study was approved by the Clinical Research Ethics Board of the University of British Columbia and the Fraser Health Research Ethics Board. The current research was approved by the Simon Fraser University Office of Research Ethics.

Table 3. Sample Characteristics

Characteristic	n (%) of 68	Mean (SD)	Median (IQR)	Range
Age		22.7 (6.7)	20.0 (7)	15 – 50
Years of education		11.7 (2.1)	12.0 (3)	7 – 17
Premorbid IQ (NAART FSIQ)		101.8 (8.5)	100.0 (12)	86 – 118
Current IQ (K-BIT IQ)		97.3 (10.0)	99.0 (14)	65 –120
Symptoms (PANSS)				
Negative		13.3 (4.7)	12.0 (6)	7 – 27
Positive		11.4 (4.2)	10.0 (6)	7 – 24
General		29.6 (8.1)	28.0 (13)	16 – 49
Total		54.3 (14.0)	54.0 (21)	31 – 93
Diagnosis				
Schizophrenia	37 (54.4)			
Schizoaffective	11 (16.2)			
Schizophreniform	2 (2.9)			
Bipolar disorder	9 (13.2)			
Major depressive disorder	2 (2.9)			
Brief psychotic disorder	1 (1.5)			
Delusional disorder	2 (2.9)			
Psychotic disorder NOS	4 (5.9)			
Medication				
Risperidone	29 (42.6)			
Olanzapine	18 (26.5)			
Quetiapine	4 (5.9)			
Clozapine	1 (1.5)			
Haloperidol	2 (2.9)			
No antipsychotics	17 (25.0)			
Benztropine	3 (4.4)			
Antidepressants	21 (30.9)			
Mood stabilizers	13 (19.1)			

Measures

Spatial working memory was measured with the Cambridge Neuropsychological Testing Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996) Spatial Working Memory task (total number of "within" errors; see Appendix B). Verbal working memory was measured with a verbal working memory index composed of the Digit Span and Letter Number Sequencing subtests of the Wechsler Adult Intelligence Scale – III (WAIS-III; Wechsler, 1997a). In this study, all index scores were calculated by averaging standardized scores (z-scores). A verbal LTM index was composed of the California Verbal Learning Test, 2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) Long Delay Free Recall and the Wechsler Memory Scale – III (WMS-III; Wechsler, 1997b) Logical Memory Delayed Recall. A motor functioning index was composed of the Grooved Pegboard test (Matthews & Klove, 1964) average completion time using the dominant and non-dominant hand, and the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard, Ross-Chouinard, Annable, & Jones, 1980) Parkinsonism score.

Premorbid IQ was estimated with the North American Adult Reading Test (NAART; Blair & Spreen, 1989), and current IQ was estimated with the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990). Psychiatric symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) positive and negative components suggested by Lindenmayer, Bernstein-Hyman, and Grochowski (1994). Depressive symptoms were measured with the sum of depression, somatic concern, anxiety, and guilt items on the PANSS (El Yazaji et al., 2002). Further information about all of these measures is included in Appendix B.

Data Analysis

Receptor load estimates. Anticholinergic load was estimated for each participant based on medication dose and the pharmacological index of relative anticholinergic potencies of psychiatric medications developed by Minzenberg and colleagues (2004). Minzenberg's (2004) index reports the dose of each medication that is equivalent in anticholinergic effect to 1mg of benztropine. Each participant's medication dose was divided by the dose of that medication that is equivalent to 1mg of benztropine to yield an anticholinergic load. Thus, the anticholinergic load for each participant is the amount of benztropine that is estimated to have an equivalent anticholinergic effect to the participant's medication. For participants taking more than one type of medication with anticholinergic effects, the anticholinergic loads of the different medications (including antipsychotics, anticholinergics, and antidepressants) were summed.

The current study extended the methods of Minzenberg and colleagues by developing a 5-HT_{2A} antagonism potency index, a D_1 antagonism potency index, and a D_2 antagonism potency index, based on published reports of in vitro brain 5-HT_{2A} receptor antagonism, D_1 antagonism, and D_2 antagonism. These antagonist loads express the amount of loxapine that has equivalent 5-HT_{2A} antagonism, D_1 antagonism, or D_2 antagonism to the participant's medication dose. Appropriate reports were provided by and identified through the National Institute of Mental Health's Psychoactive Drug Screening Program K_i database[13] (Bonhaus et al., 1997; Burstein et al., 2005; Kroeze et al., 2003; Seeman, 2001; Seeman, Corbett, & Van Tol, 1997; Vanover et al., 2004; see

Appendix B for further details). Following Minzenberg's (2004) technique, a 5-HT_{2A} antagonist load, a D_1 antagonist load, and a D_2 antagonist load were estimated for each participant. For example, the ratio of risperidone's affinity for 5-HT_{2A} receptors and loxapine's affinity for 5-HT_{2A} receptors was calculated, and each participant's dose of risperidone was divided by that ratio to yield the amount of loxapine that the participant's medication is equivalent to in 5-HT_{2A} antagonism. The same calculations were carried out for each antipsychotic medication, for 5-HT_{2A} antagonism, D_1 antagonism, and D_2 antagonism.

In addition to receptor antagonist load estimates, receptor occupancy estimates were investigated as an alternative measure of D_2 antagonism that may be more directly associated with medication impact on receptor functioning. Occupancies were estimated by $occ_{max} * dose / (dose + ED_{50})$, where $dose$ is the participant's medication dose, occ_{max} is the maximum possible occupancy and ED_{50} is the dose of medication required to occupy 50% of the maximum possible occupancy (Kapur, Zipurksy, & Remington, 1999). Values of occ_{max} and ED_{50} were retrieved from published reports of human PET studies (Bernardo et al., 2001; Kapur et al., 1999; Tauscher-Wisniewski et al., 2002).[14]

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[13] K_i determinations were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA.
For experimental details please refer to the PDSP web site http://pdsp.med.unc.edu/ and click on "Binding Assay" or "Functional Assay" on the menu bar.

[14] Occupancy was not estimated for other receptors because sufficient published PET studies were not available.

Statistical procedures. Regression analyses were conducted to evaluate the impact

of medication properties on neuropsychological functions and negative symptoms.[15] A

series of hierarchical analyses predicting verbal LTM and motor functioning was

conducted to test Hypothesis 1, i.e., that higher anticholinergic load is associated with

worse verbal LTM but is not associated with motor functioning, and Hypothesis 2, i.e.,

that higher D_2 antagonist load is associated with worse motor functioning but is not

associated with verbal LTM. A second series of hierarchical analyses predicting working

memory and negative symptoms was conducted to test Hypothesis 3, i.e., that higher D_1

antagonist load is associated with worse working memory and more severe negative

symptoms, and Hypothesis 4, i.e., that higher 5-HT_{2A} antagonist load is associated with

better working memory and less severe negative symptoms.[16]

Background variables known to be associated with cognition (gender, age, premorbid

IQ, smoking status, diagnosis,[17] antidepressant medication status, mood stabilizer status,

positive symptoms, negative symptoms, and depressive symptoms) were evaluated by

inspecting scatter plots and zero-order correlations[18] with the dependent variables.

Background variables that were associated with the dependent variables ($p<.10$) were

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[15] Preliminary analyses indicated that correlations among the receptor loads (i.e., multicollinearity; see Table A2) would be unacceptably high: the standard errors of the regression coefficients would up to 1.8 times higher due to multicollinearity, relative to what they would be if all of the predictors were uncorrelated (Cohen et al., 2003). In order to reduce multicollinearity and thus increase the accuracy of the regression results, Hypotheses 1 and 2 were analyzed separately from Hypotheses 3 and 4. Consequently, some of the hypothesized dissociations were not evaluated. Specifically, the impacts of anticholinergic load and D_2 load on working memory and negative symptoms were not tested, and the impacts of D_1 load and 5-HT_{2A} load on verbal long-term memory and motor functioning were not tested.

[16] Participants taking antidepressant medications were excluded from the second series of analyses because these medications act as serotonin reuptake inhibitors and thus cannot be accounted for in serotonergic load calculations.

[17] Schizophrenia spectrum diagnoses were contrasted against all other diagnoses.

[18] Pearson product moment correlations were used for continuous variables, and point biserial correlations were used for dichotomous variables.

entered on Step 1. In the analysis of variables predicting negative symptoms, Parkinsonism was also entered on Step 1 to control for illness severity and medication motor side effects. The hypothesized load and occupancy variables were entered on Step 2. Log transformation was applied to some variables in order to improve normality and reduce outliers. Non-significant predictors were dropped from the analyses. For each series of analyses, a sequential Bonferroni correction was applied to maintain an experiment-wise significance level of .05. Further details of the statistical procedures are outlined in Appendix C.

Results

Medication Impact on Verbal LTM and Motor Functioning

Anticholinergic load, D_2 load, D_2 occupancy, D_1 load, and 5-HT$_{2A}$ load were calculated for each participant (see Table 4). Zero-order correlations of the independent variables with verbal LTM and motor functioning are listed in Table 5.[19] Regression results are summarized in Table 6.[20] Background variables accounted for 17% of the variance in verbal LTM. In particular, higher premorbid IQ and female gender were associated with better verbal LTM. An additional 19% of variance was explained by introducing anticholinergic load into the model. Higher anticholinergic load was associated with poorer verbal LTM. In contrast, D_2 load was not associated with verbal LTM.

Table 4. Medication Impact on Receptors

Type of impact	Mean (SD)	Median (IQR)	Range
Anticholinergic load[†]	1.0 (6.1)	0.0 (.6)	0 – 50.0
D_2 load[‡]	12.6 (15.7)	5.7 (18.7)	0 – 62.5
D_2 occupancy (%)	43.7 (29.7)	50.6 (.7)	0 – 83.0
5-HT$_{2A}$ load[‡]	42.1 (70.4)	23.1 (53.3)	0 – 495.7
D_1 load[‡]	6.6 (15.3)	1.5 (6.9)	0 – 114.3

[†] Expressed in mg benztropine equivalent

[‡] Expressed in mg loxapine equivalent

[19] Of the 68 participants, marijuana smoking status was not reported for one participant and mood stabilizer use status was not reported for four participants.

[20] All associations remained significant after sequential Bonferroni correction.

Table 5. Correlations of Independent Variables with Verbal LTM and Motor Functioning

Independent variable	Verbal LTM	Motor functioning
Anticholinergic load	-.42*	-.16
D_2 load	-.08	-.45*
D_2 occupancy	-.34*	-.18
Premorbid IQ	.31*	.11
Negative symptoms	-.38*	-.15
Gender (0 = M; 1 = F)	.26*	.23*
Diagnosis (0 = scz spectrum; 1 = other)	.23*	.25*
Marijuana (0 = no; 1 = yes[††])	-.14	.23*
Mood stabilizers (0 = no; 1 = yes)	.12	-.24*

Note. Higher scores on neuropsychological measures represent better performance. Higher scores on symptom measures represent more severe symptoms.

* $p<.10$

[††] Any marijuana use reported in the past several months

Table 6. Regression Analyses for Variables Predicting Verbal LTM and Motor Functioning

Variable	B	SE B	ß	p	R^2	ΔR^2
Analysis 1: Verbal LTM						
Step 1					.17	.17*
Gender	.50	.21	.28	.02		
Premorbid IQ	.03	.01	.30	.01		
Step 2					.36	.19*
Gender	.52	.18	.29	.01		
Premorbid IQ	.04	.01	.37	<.01		
Anticholinergic load	-.75	.17	-.47	<.01		
Analysis 2: Motor functioning						
Step 1					.21	.21*
Gender	.61	.20	.36	.01		
Marijuana	.38	.19	.24	.05		
Mood stabilizers	-.50	.23	-.26	.03		
Step 2					.34	.13*
Gender	.58	.18	.35	.01		
Marijuana	.40	.17	.25	.02		
Mood stabilizers	-.51	.21	-.26	.02		
D_2 load[†]	-.49	.14	-.36	.01		

Note. N = 68 for Analysis 1; N=63 for Analysis

* $p<.01$

[†] log transformed

Background variables accounted for 21% of the variance in motor functioning. Female participants and participants who smoked marijuana had better motor functioning. Participants who were taking mood stabilizers had poorer motor functioning.

D_2 load accounted for an additional 13% of the variance. Specifically, higher D_2 load was associated with poorer motor functioning. D_2 occupancy was correlated with verbal LTM, but was not reliably associated with either verbal LTM or motor functioning.[21] Anticholinergic load was not associated with motor functioning.

Medication Impact on Working Memory and Negative Symptoms

Forty-five participants who were not taking antidepressant medications were included in an analysis of the impacts of D_1 load and 5-HT_{2A} load on working memory and negative symptoms.[22] Zero-order correlations of the independent variables with working memory and negative symptoms are listed in Table 7. Spatial working memory was not associated with D_1 load or 5-HT_{2A} load. Verbal working memory was associated with 5-HT_{2A} load. The association between verbal working memory and 5-HT_{2A} load did not remain significant after sequential Bonferroni correction (a p-value < .008 would be required for significance), but the regression results are summarized in Table 8 so that the reader may consider a possible Type II error. In this model, 11% of the variance in verbal working memory was explained by 5-HT_{2A} load. Higher 5-HT_{2A} load was associated with poorer verbal working memory. In contrast, D_1 load was not associated with verbal working memory.

Although D_1 load was associated with negative symptom severity in the zero-order correlation analysis, that association did not remain when background variables were

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[21] Although there were significant zero-order correlations between D_2 occupancy and verbal LTM, further analysis revealed no associations when un-medicated participants were excluded from the sample.

[22] Of the 45 participants included, one participant did not report tobacco or marijuana smoking status, one participant did not complete the spatial working memory task, and one participant did not receive a negative symptom rating.

accounted for in the regression model (not shown). $5\text{-}HT_{2A}$ load was marginally

associated with negative symptom severity in the regression, but that association was

driven by several outlying data points and thus was not reliable.

Table 7. Correlations of Independent Variables with Working Memory and Negative Symptoms

Independent variable	Verbal working memory	Spatial working memory	Negative symptoms
$5\text{-}HT_{2A}$ load	-.35*	-.17	-.01
D_1 load	-.09	-.16	.26*
Age	.13	-.27*	.14
Tobacco (0 = no; 1 = yes[†])	-.25	-.24	.28*
Marijuana (0 = no; 1 = yes[††])	.03	-.10	.38*
Premorbid IQ	.40*	.22	-.19
Diagnosis (0=scz spectrum; 1 = other)	.34*	.00	-.36*

Note. Participants taking antidepressant medications were excluded from this sample
* $p<.10$
[†] Reported smoking any cigarettes in the past several months
[††] Reported smoking any marijuana in the past several months

Table 8. Regression Analysis for Variables Predicting Verbal Working Memory

Variable	B	SE B	ß	p	R^2	ΔR^2
Step 1					.16	.16*
Premorbid IQ	.05	.02	.40	.01		
Step 2					.27	.11*
$5\text{-}HT_{2A}$ load[†]	-.41	.17	-.33	.02		

Note. N = 45.
* $p<.05$
[†] log transformed

Interestingly, routine inspection of scatter plots revealed that the association between

$5\text{-}HT_{2A}$ load and verbal working memory may be driven by an effect present in tobacco

smokers ($r = -.55$) but not apparent in non-smokers ($r = -.06$). Furthermore, the

correlation between D_1 load and negative symptom severity appeared to be driven by an

effect present in participants who do not smoke marijuana ($r = .62$), but not in those who

do ($r = .09$). However, the small sample size precluded statistical evaluation of interactions between tobacco and marijuana smoking status and receptor antagonist loads. Because tobacco and marijuana can increase dopamine levels in the prefrontal cortex (Jentsch, Andrusiak, Tran, Bowers, & Roth, 1997; Shearman, Rossi, Sershen, Hashim, & Lajtha, 2005), these factors were further explored in a posteriori analysis.

Regression was used to investigate the associations between receptor loads and spatial working memory, verbal working memory, and negative symptoms in subgroups of the sample, divided according to tobacco and marijuana smoking status. Table 9 presents standardized regression coefficients for the following subgroups: 1) tobacco smokers, 2) marijuana smokers, 3) participants who smoke tobacco and/or marijuana regularly,[23] 4) non-tobacco-smokers, 5) non-marijuana-smokers, and 6) participants who do not smoke tobacco and do not smoke marijuana regularly.

Spatial working memory was not associated with D_1 load or 5-HT_{2A} load in any of the subgroups. Analysis of variables predicting verbal working memory revealed that neither D_1 load nor 5-HT_{2A} load was associated with verbal working memory in non-smokers. However, in tobacco smokers and regular marijuana smokers, higher 5-HT_{2A} load was associated with poorer verbal working memory.

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[23] At least several times per week.

Table 9. Standardized Regression Coefficients by Tobacco and Marijuana Smoking Status for Variables Predicting Working Memory and Negative Symptoms

Receptor antagonist load	Smokers			Non-smokers		
	Tobacco (n = 20)	Marijuana (n = 23)	Tobacco and/or frequent marijuana (n = 24)	Tobacco (n = 24)	Marijuana (n = 21)	Tobacco nor frequent marijuana (n = 20)
Analysis 1: Spatial working memory						
D_1 load	-.12	-.19	-.14	-.26	.16	.31
5-HT$_{2A}$ load	-.39	-.25	-.35	-.01	-.16	.00
Analysis 2: Verbal working memory						
D_1 load	-.16	-.09	-.06	.03	-.03	-.05
5-HT$_{2A}$ load	-.55**	-.28	-.48**	-.06	-.38	-.04
Analysis 3: Negative symptoms						
D_1 load[†]	.23	.09	.23	.65**	.62***	.58**
5-HT$_{2A}$ load[†]	-.08	-.14	-.08	-.55**	-.74***	-.59**

* *p*<.10

***p*<.05

*** *p*<.01

[†] log transformed

Note. To control for background variables associated with each dependent variable, age was entered in Step 1 of Analysis 1, premorbid IQ and diagnosis (0 = scz spectrum; 1 = other) were entered in Step 1 of Analysis 2, and diagnosis was entered in Step 1 of Analysis 3.

In the groups of non-smokers, higher 5-HT$_{2A}$ load was associated with less severe negative symptoms; conversely, higher D_1 load was associated with more severe negative symptoms. In smokers, however, neither load was associated with negative symptoms. A summary of the results of each hypothesis is presented in Table 10.

Table 10. Summary of Results

Hypothesis	Results
1	Higher anticholinergic load was associated with poorer verbal LTM, but was not associated with motor functioning.
2	Higher D_2 load was associated with poorer motor functioning, but was not associated with verbal LTM. D_2 occupancy was not associated with motor functioning or verbal LTM.
3	D_1 load was not associated with spatial working memory or verbal working memory. In the full sample, D_1 load was not associated with negative symptom severity. In non-smokers, higher D_1 load was associated with more severe negative symptoms.
4	5-HT_{2A} load was not associated with spatial working memory. In the full sample, 5-HT_{2A} load was not associated with negative symptom severity, and was associated with poorer verbal working memory, although this association did not remain significant after Bonferroni correction. In smokers, higher 5-HT_{2A} load was associated with poorer verbal working memory. In non-smokers, higher 5-HT_{2A} load was associated with less severe negative symptoms.

Discussion

The current study investigated links between antipsychotic medication properties and specific neuropsychological abilities and psychiatric symptoms. The findings of Minzenberg and colleagues (2004), generated from a chronic psychosis sample, were extended to an FEP sample. In addition to replicating Minzenberg and colleagues' (2004) result, the current study employed parallel techniques to develop scales of D_1 load, D_2 load and 5-HT_{2A} load.

In accordance with Hypotheses 1 and 2, higher anticholinergic load was associated with poorer verbal LTM but was not associated with motor functioning, and higher D_2 load was associated with poorer motor functioning but was not associated with verbal LTM. D_2 occupancy was investigated as an alternative measure of medication impact on D_2 receptors, but was not reliably associated with motor functioning or verbal LTM.

These findings suggest that the previously identified association between anticholinergic load and verbal LTM is not limited to chronic schizophrenia spectrum disorder samples, but extends to an FEP sample as well.

The observed association between D_2 load and motor functioning suggests that D_2 load contributes to the profile of fine and gross motor side effects seen in patients treated with antipsychotic medications. Indeed, these anticholinergic and D_2 antagonist loads appear to have specific and dissociable effects on neuropsychological functioning.

Notably, D_2 occupancy was not associated with motor functioning. Several factors may account for this unexpected finding. First, load and occupancy estimates may capture different aspects of medication impact on D_2 receptors. Indeed, occupancy estimates rely on imaging studies that provide a snapshot of receptor occupancy some

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hours after the previous dose, while load estimates are not tied to any specific time. The relative differences between antipsychotics on the estimated D_2 occupancy is dependent upon the time between the most recent dose and the brain scan, because occupancy levels peak at different times for different antipsychotics (e.g., Saller & Salama, 1993). Thus it is possible that impacts at some time points could be captured by load estimates but not by occupancy estimates.

Another important consideration is that D_2 occupancy estimates for olanzapine do not appear to align with D_2 load estimates when compared to other drugs. For example, doses of olanzapine are estimated to have similar D_2 occupancy compared to risperidone but much lower D_2 load. It is possible that the previous research linking D_2 occupancy and motor functioning in patients taking haloperidol, clozapine, and risperidone may not be applicable to patients taking olanzapine.

Finally, since medication doses were relatively low in this sample, it is possible that occupancy in this sample did not reach the threshold at which severe motor symptoms tend to appear. Virtually all of the participants in the current sample had estimated D_2 occupancy below 80%, which has been suggested as a threshold for extrapyramidal symptoms (Farde et al., 1992). The detection of an effect of D_2 load despite low occupancy in this sample suggests that D_2 load may be a particularly sensitive measure of impact on D_2 receptors. However, this link between D_2 load and motor functioning should be considered preliminary until it is replicated in a larger sample.

Tests of Hypotheses 3 and 4 revealed a more complex picture. Although higher D_1 load was expected to be associated with poorer working memory and more severe negative symptoms, it was not associated with these variables. Higher $5\text{-}HT_{2A}$ load was expected to increase prefrontal dopamine and therefore be associated with better working

memory and less severe negative symptoms. However, $5\text{-}HT_{2A}$ load was not associated with spatial working memory or negative symptoms, and notably, higher $5\text{-}HT_{2A}$ load was associated with *poorer* verbal working memory.

Routine inspection of scatter plots suggested that tobacco and marijuana smoking status were likely motivating the effects of D_1 load and $5\text{-}HT_{2A}$ load in these analyses. Although the power limitations did not allow interactions to be evaluated in the planned regression model, separate analyses of several subgroups were conducted to illustrate the pattern of results. These exploratory analyses indicated that in participants who did not smoke tobacco and participants who did not frequently smoke marijuana, higher D_1 load was associated with more severe negative symptoms as predicted. In contrast, in smokers, D_1 load was not associated with negative symptom severity. D_1 load was not reliably associated with working memory in any of the subgroups.

The observed impact of D_1 load on negative symptoms may be reconciled with the original hypothesis by taking into consideration the associations of marijuana and low-dose nicotine administration with increased prefrontal dopamine (Shearman et al., 2005; Voruganti et al., 2001; see Figure 1). In non-smokers, D_1 antagonism may worsen negative symptoms by exacerbating the dopaminergic hypofunction that is thought to underlie negative symptoms. However, tobacco or marijuana smokers may have higher baseline dopamine in the prefrontal cortex, and may thus be less susceptible to impact from D_1 antagonism. Interestingly, in this model higher D_1 load would also be expected to be associated with poorer working memory in non-smokers. This effect was not observed in the current sample.

Hypothesis 4 predicted that higher $5\text{-}HT_{2A}$ load would be associated with less severe negative symptoms. This was confirmed only in non-smokers (not in tobacco smokers or

frequent marijuana smokers). Additionally, contrary to the prediction, higher $5\text{-}HT_{2A}$ load was associated with worse verbal working memory, but only in tobacco smokers and frequent marijuana smokers. Effects of $5\text{-}HT_{2A}$ load were hypothesized based on evidence that $5\text{-}HT_{2A}$ antagonism in the context of D_2 antagonism increases prefrontal dopamine release.

Figure 1. Effects of D_1 Load on Working Memory and Negative Symptoms
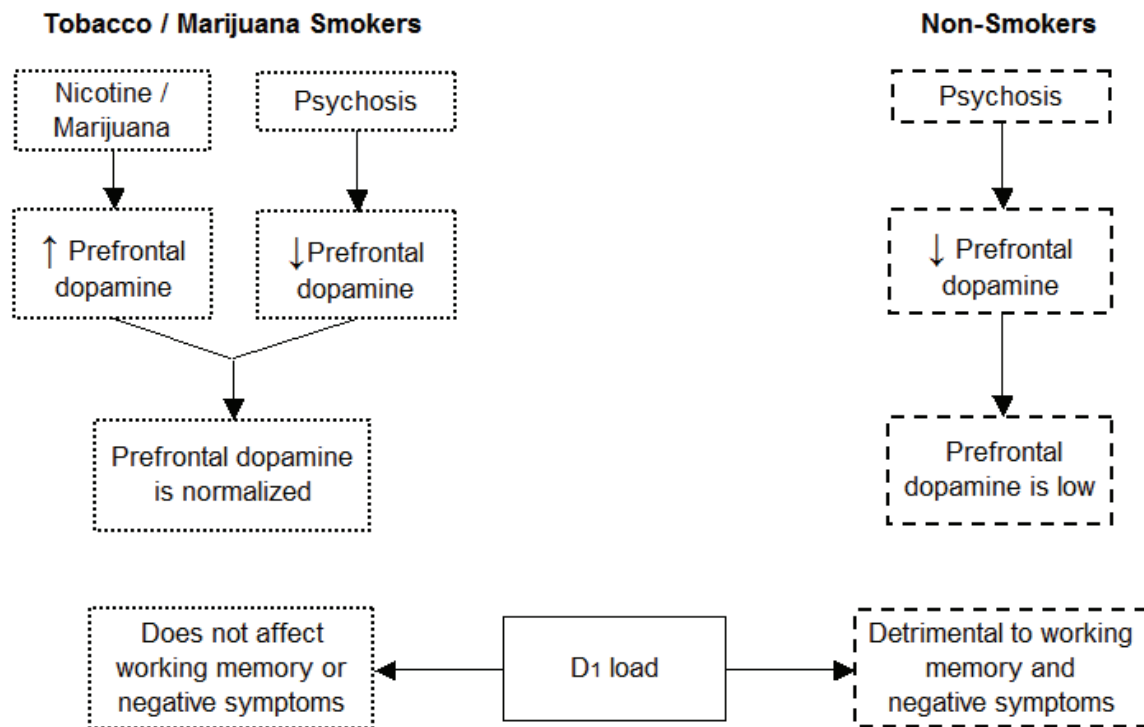
Note. Psychosis is associated with low prefrontal dopamine. However, nicotine and marijuana are known to increase prefrontal dopamine release. For non-smokers with FEP, shown on the right side of the figure, D_1 load is expected to be detrimental to working memory and negative symptoms. However, smokers with FEP, shown on the left side of the figure, are thought to have more normal levels of prefrontal dopamine and may thus be less susceptible to D_1 load.

The observed effects may again be reconciled with the original hypothesis by taking into consideration the impacts of nicotine and marijuana on dopamine levels as well as a direct impairing effect (not mediated by dopamine release) of $5\text{-}HT_{2A}$ antagonism on working memory (Williams, Rao, & Goldman-Rakic, 2002; see Figure 2). In participants

who do not smoke tobacco or marijuana, 5-HT$_{2A}$ antagonism may improve negative symptoms by increasing prefrontal dopamine release. However, smokers and frequent marijuana users may benefit less from the same dopamine release because of higher baseline dopamine. In participants who do not smoke tobacco or marijuana, 5-HT$_{2A}$ antagonism may directly impair working memory while simultaneously indirectly improving working memory by increasing prefrontal dopamine, resulting in no net association between 5-HT$_{2A}$ load and working memory. However, the same increase in prefrontal dopamine may be less beneficial to working memory in tobacco smokers and frequent marijuana smokers, resulting in a net impairing effect of 5-HT$_{2A}$ load on working memory. In this model, higher 5-HT$_{2A}$ load would be expected to be associated with worse spatial and verbal working memory in smokers. However, 5-HT$_{2A}$ load is not associated with spatial working memory in the current sample.

Figure 2. Effects of 5-HT$_{2A}$ Load on Working Memory and Negative Symptoms
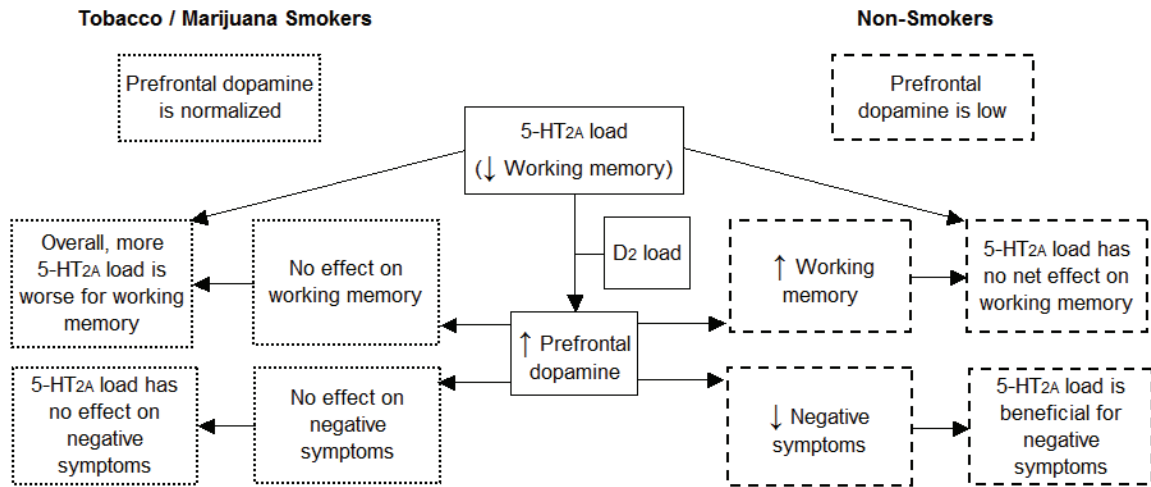
Note. 5-HT$_{2A}$ load is expected to be detrimental to working memory, but (in the context of D$_2$ load) is also expected to increase prefrontal dopamine release. Non-smokers with FEP, shown on the right side of the figure, are thought to have low prefrontal dopamine. In this group, increased prefrontal dopamine release is thought to improve working memory and negative symptoms. However, because of the direct detrimental effect of 5-HT$_{2A}$ antagonism on working memory, there should be no net effect of 5-HT$_{2A}$ load on working memory. Smokers with FEP, shown on the left side of the figure, are thought to have more normal levels of prefrontal dopamine; thus, an increase in prefrontal dopamine release would not be beneficial in this group.

Although the current findings of the impact of D$_1$ load and 5-HT$_{2A}$ load on working memory and negative symptoms are largely consistent with the model depicted in Figures 1 and 2, they should be considered preliminary. The observed effects were not hypothesized a priori, and although the effect sizes are relatively large, the sample sizes are small. Replication in a larger sample is warranted.

Conclusion

The current study supports the validity of Minzenberg and colleagues' (2004) anticholinergic load scale as a predictor of verbal LTM functioning in patients with psychosis. It further suggests that parallel techniques may be employed to elucidate specific and dissociable effects of other antipsychotic medication properties on neuropsychological functions and psychiatric symptoms. The method of calculating estimated receptor antagonist loads enables a variety of medications to be evaluated on common scales of impact on dopaminergic, serotonergic, and cholinergic receptors. This allows analysis at the level of receptor blockade, independent of the type of medication. This strategy may be particularly valuable in predicting the effects of polypharmacy, because receptor loads can be summed across medications.

Findings in the current FEP sample suggest that in addition to high anticholinergic load being detrimental to verbal LTM, high D_2 load may be detrimental to motor functioning. Preliminary findings suggest that high D_1 load may increase the severity of negative symptoms in groups who do not smoke tobacco or marijuana. Furthermore, high 5-HT_{2A} load may decrease the severity of negative symptoms in non-smokers, but may be detrimental to verbal working memory in tobacco smokers and frequent marijuana smokers.

Understanding the effects of antipsychotic medications at an early stage of illness is critically important for two reasons. First, the effects of antipsychotic medications may differ in FEP versus chronic samples because they are inherently different – FEP samples tend to be younger, with only limited exposure to antipsychotic medications, and they contain a subgroup that will not remain chronically ill. Second, the effects and side

effects of antipsychotic medications specifically during the first episode may be pivotal to medication adherence, which is associated with functional outcome (Dunayevich et al., 2007).

Possible directions for future research include replication of the current findings in new samples and with more diverse medications. Investigation of other receptors that are affected by antipsychotic medications and are associated with cognition, such as the 5-HT$_{2C}$ receptor or the α-1 adrenergic receptor, may also prove fruitful.

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Appendix A

Table A 1. Medication Efficacy for Negative Symptoms: Meta-Analytic Effect Sizes

Study	Results	Effect Size	k	Total N
		Risperidone		
Davis & Chen, 2002	Risperidone > Typicals	Cohen's *d* = .20 (95% CI: 0.13 to 0.28)	15	3363
Geddes, Freemantle, Harrison, & Bebbington, 2000	Risperidone > Typicals	Cohen's *d* = .15 (95% CI: .03 to .27)	6	1611
Leucht et al., 2009	Risperidone > Typicals	Hedges' *g* = .13 (95% CI: .06 to .21)	30	3455
Carman, Peuskens, & Vangeneugden, 1995	Risperidone > Typicals	odds ratio = 1.43	6	675
Leucht, Pitschel-Walz, Abraham, & Kissling, 1999	Risperidone > Typicals	*r* = .04	7	3000
		Olanzapine		
Geddes, Freemantle, Harrison, & Bebbington, 2000	Olanzapine > Typicals	Cohen's *d* = .19 (95% CI: .11 to .27)	4	2471
Leucht et al., 2009	Olanzapine > Typicals	Hedges' *g* = .32 (95% CI: .16 to .47)	24	4178
Leucht, Pitschel-Walz, Abraham, & Kissling, 1999	Olanzapine > Haloperidol	*r* = .08	3	2993
		Quetiapine		
Geddes, Freemantle, Harrison, & Bebbington, 2000	Quetiapine not different from typicals	Cohen's *d* = .23 (95% CI: -.07 to .54)	2	449
Leucht et al., 2009	Quetiapine not different from typicals	Hedges' *g* = 0.0 (95% CI: -.09 to .09)	10	1926
Leucht, Pitschel-Walz, Abraham, & Kissling, 1999	Quetiapine < Typicals	*r* = -.12	2	487

Study	Results	Effect Size	k	Total N
	Clozapine			
Wahlbeck, Cheine, Essali, & Adams, 1999	Clozapine > Typicals	Cohen's d = .4 (95% CI: .1 to .8)	4	164
Leucht et al., 2009	Clozapine > Typicals	Hedges' g = .27 (95% CI: .13 to .42)	17	1603
	Amisulpiride			
Leucht et al., 2009	Amisulpiride > Typicals	Hedges' g = .27 (95% CI: .14 to .40)	10	929
	Aripiprazole			
Leucht et al., 2009	Aripiprazole not different from typicals	Hedges' g = .09 (95% CI: -.01 to .19)	5	1278
	Sertindole			
Leucht et al., 2009	Sertindole not different from typicals	Hedges' g = .04 (95% CI: -.01 to -.22)	2	574
	Ziprasidone			
Leucht et al., 2009	Ziprasidone not different from typicals	Hedges' g =.09 (95% CI: -.11 to .29)	3	691
	Zotepine			
Leucht et al., 2009	Zotepine not different from typicals	Hedges' g = .23 (95% CI: 0.0 to .46)	5	450

Table A 2. Intercorrelations Among Receptor Loads.

	5-HT$_{2A}$ antagonist load	Anticholinergic (M$_1$) load	D$_1$ antagonist load
Anticholinergic (M$_1$) load	.36**		
D$_1$ antagonist load	.12	.79**	
D$_2$ antagonist load	.75**	.44**	.28*

* p < .05
** p < .01

Appendix B

Diagnoses were made according to *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) criteria. Information for diagnoses was obtained from a clinical interview of the patient and inquiry with (where possible) at least one family member by a research psychiatrist, and the Structured Clinical Interview for DSM-III-R (Spitzer, Williams, Gibbon, & First, 1990). Final diagnoses were made at a consensus conference, using all available clinical and research information and DSM-IV criteria. Each participant's level of completed education was indexed according to the guidelines offered by Heaton, Miller, Taylor, and Grant (2004). Neurocognitive and psychiatric symptom assessments were carried out by research assistants under the supervision of a clinical psychologist at baseline and again at a follow-up session 9-12 months later, at Peace Arch Hospital in White Rock, BC.

Measures

Working memory. Spatial working memory was measured with the CANTAB Spatial Working Memory task (Fray, Robbins, & Sahakian, 1996), a computerized visual search task in which the participant must find tokens under 4, 6, or 8 squares, without looking under the same square more than once. After a token is found under a square, the participant must look for another token which may be found under any square except those where tokens have already been found. The number of 'within' errors, occurring when the subject looks under a square already found to be empty during the current search, was analyzed. The test/re-test reliability measured by Pearson's product-moment

correlation coefficient (*r*) is .71 for the Spatial Working Memory task (Harrison et al., 1998).

Verbal working memory was measured with the Digit Span and Letter Number Sequencing subtests of the WAIS-III (Wechsler, 1997a). These highly reliable measures are sensitive to first-episode schizophrenia (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). The test/re-test reliabilities (*r*s) for Digit Span and Letter number sequencing are .83 and .75, respectively (The Psychological Corporation, 1997).

Verbal LTM. Verbal LTM was measured with the CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) and the Logical Memory subtest of the WMS-III (Wechsler, 1997b). The CVLT-II is a widely used list-learning measure that indicates a large deficit in first-episode schizophrenia (Mesholam-Gately et al., 2009). The Logical Memory subtest, also sensitive to first-episode schizophrenia (Mesholam-Gately et al., 2009) was analyzed as an additional measure of verbal LTM to increase reliability. The test/re-test reliability (*r*) for CVLT long delay free recall is .88 (Delis et al., 2000), and the test/re-test reliability (*r*) for Logical Memory is .79 (The Psychological Corporation, 1997).

Motor functioning. Motor functioning was measured by the Grooved Pegboard test (Matthews & Klove, 1964) and the ESRS Parkinsonism score (Chouinard, Ross-Chouinard, Annable, & Jones, 1980). The Grooved Pegboard test is a widely used measure of motor speed and dexterity that is highly sensitive to first-episode schizophrenia (Mesholam-Gately et al., 2009) and dopaminergic nigrostriatal denervation in Parkinson's disease (Bohnen, Kuwabara, Constantine, Mathis, & Moore, 2007). The ESRS is a physician-rated scale designed to assess drug-induced movement disorders. The Parkinsonism score includes ratings of tremor, impaired gait/posture, postural instability, rigidity, reduced facial expression/speech, bradykinesia, and sialorrhea. The

test/re-test reliability (*r*) of the Grooved Pegboard test is .86 (Dikmen, Heaton, Grant, & Temkin, 1999), and the inter-rater reliability (intra-class correlation coefficient) of ESRS scores ranges between .80 and .97 (Chouinard et al., 1980).

Estimated current and premorbid IQ. The K-BIT (Kaufman & Kaufman, 1990) was used to estimate current intellectual functioning, and the NAART (Blair & Spreen, 1989) was used to estimate premorbid intellectual functioning. The NAART is correlated with intelligence test scores and academic achievement in healthy participants (Blair & Spreen, 1989). The test/re-test reliability (*r*) for the K-BIT is greater than .90 (Kaufman & Kaufman, 1990) and for the NAART is .92 (Raguet, Campbell, Berry, Schmitt, & Smith, 1996).

Psychiatric symptoms. Symptom severity was measured with the PANSS (Kay, Fiszbein, & Opler, 1987). The PANSS includes a priori positive and negative syndrome scales, but numerous principle component analysis studies have identified five factors explaining slightly more than 50% of the total variance (e.g., Emsley, Rabinowitz, & Torreman, 2003; Lindenmayer, Bernstein-Hyman, & Grochowski, 1994; Lindström & von Knorring, 1993). The positive component and negative component suggested by Lindenmayer and colleagues (1994) were analyzed. The internal consistency as measured by Chronbach's alpha is .80 for the positive component, and .86 for the negative component. Depressive symptoms were measured with the depression, somatic concern, anxiety, and guilt items from the PANSS. This item subset has been supported by principle component analysis and is highly correlated with the Calgary Depression Scale for Schizophrenia (Addington, Addington, & Matickatyndale, 1993; El Yazaji et al., 2002).

K$_i$ value selection. K$_i$ values were taken from reports of studies using human cloned receptors. Radioligands were [^{3}H]ketanserin for 5-HT$_{2A}$ studies, [^{3}H]SCH23390 for D$_1$ studies, and [^{3}H]raclopride for D$_2$ studies. PDSP certified data was selected where available; otherwise the average K$_i$ value across all appropriate reports was taken.

Appendix C

Data points with absolute-value z-scores greater than 3.29 were considered outliers and adjusted to the next-highest value. Multivariate outliers were identified by examining scatter plots of centred leverage values, externally studentized residuals, DFFITS, and DFBETAS (Cohen et al., 2003). The influence of outliers was also examined by re-analyzing the data with outliers excluded. Effects were considered robust only if the regression coefficients did not vary widely 1) when outliers were removed, 2) when un-medicated participants were excluded, 3) when participants with diagnoses other than schizophrenia spectrum disorder were excluded, 4) when participants with a history of head injury with an associated loss of consciousness of more than 5 minutes were excluded, 5) when participants taking benzodiazepines were excluded, 6) when participants who reported using illicit drugs other than marijuana were excluded, and in the case of log transformed variables, 7) when similar results were obtained using untransformed variables.

For each regression analysis, scatter plots were examined to check the assumptions of correct specification of the form of the relationship and correctly specified relevant predictors. The homoscedasticity of residuals assumption was evaluated using plots of the residuals against the independent variables and the predicted dependent variable values. Where these plots indicated possible heteroscedasticity, the modified Levene test (Cohen et al., 2003) was used to determine whether the homoscedasticity assumption was met. The independence of errors assumption was checked using plots of the residuals against

the order that participants joined the study. The normality of errors assumption was

checked using normal probability (*Q-Q*) plots.