Reducing Diagnostic Uncertainty in First-Episode Psychosis: A Neuropsychological Approach to Differentiating between Cannabis-Induced and Primary Psychotic Disorders

by

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DIFFERENTIATING CANNABIS-INDUCED AND PRIMARY PSYCHOSIS

Abstract

**Background:** Cannabis use is highly comorbid with psychotic disorders, especially among young people experiencing their first episode of psychosis. The high rate of cannabis use in this population has led to uncertainty between diagnoses of *cannabis-induced* psychosis and primary psychosis, often with cannabis comorbidity (*primary* psychosis). The similarity of the clinical presentations of these disorders often renders them indistinguishable, creating difficulties in intervention and treatment. Attempts to identify differentiating features have been variable and narrow in scope, with a focus limited to self-report, patient history, and symptoms. Despite the abundance of research identifying cognitive deficits and abnormalities in eye movements and speech as core biological and neurological symptoms of primary psychotic disorders (e.g., schizophrenia), limited research has pursued such biomarkers as potential targets for differentiation in first-episode psychosis.

**Purpose:** The current study aimed to assess individuals diagnosed with either *cannabis-induced* or *primary* psychosis using cognitive, visual processing, eye movement, and speech tasks, which are each associated with well-recognized and specific deficits in primary psychotic disorders.

**Method:** Sixteen participants with *cannabis-induced* psychosis and twelve participants with *primary* psychosis were recruited in the Kingston, Ontario community. Cognitive performance, backward visual masking, pro- and anti-saccade eye movements, and semantic coherence were assessed for the first time in this population, alongside clinical symptoms, trauma, substance use, premorbid functioning, and illness insight.

**Results.** Relative to individuals with *primary* psychosis, individuals with *cannabis-induced* psychosis demonstrated significantly better performance on the pro-saccade task, a faster reaction time on both the pro- and anti-saccade task, more coherent speech, better premorbid
adjustment, more cannabis use, and a higher degree of insight into their illness. The use of these variables in a discriminant analysis successfully classified cases with 88.5% accuracy. The ability to reliably differentiate these disorders is crucial to early intervention and treatment in first-episode psychosis.
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Chapter 1

Introduction

Core Characteristics of Schizophrenia-Spectrum Disorders

Schizophrenia is a chronic and severe mental illness that manifests early in life and persists throughout the lifespan. It is associated with frequent relapses, increased mortality, and extensive cognitive, functional, psychosocial, and vocational impairments (Świtaj et al., 2012; Saha, Chant, & McGrath, 2007; Emsley, Chiliza, Asmal, & Harvey, 2013; Robinson et al., 1999). Defining features of the illness as outlined by the Diagnostic and Statistical Manual – 5th edition (DSM-5; American Psychiatric Association, 2013) include positive symptoms (e.g., delusions and hallucinations), disorganized speech, grossly disorganized or abnormal motor behaviour (e.g., catatonia), and negative symptoms (e.g., alogia, anhedonia, flattened affect). Among the negative symptoms of schizophrenia outlined by the DSM-5 is asociality, or the lack of interest in social interactions, which is tied to one’s motivation to engage with their community or social circle. Beyond this lack of interest, considerable research has demonstrated that individuals with schizophrenia display significant impairments in social cognition and social functioning (Penn, Sanna, & Roberts, 2008; Savla, Vella, Armstrong, Penn, & Twamley, 2012; Green, Horan, & Lee, 2019), which may result from a combination of both symptom interference and a lifetime of reduced opportunities for social interaction and learning (Blanchard, Park, Catalano, & Bennett, 2015; Green et al., 2018; Adery, Park, & Kim, 2017). Related to social difficulties are abnormalities in communication, such as disconnected speech and verbal underproductivity, both hallmark features of schizophrenia (Bowie, Gupta, & Holshausen, 2011). Notable areas of impairment in communication include semantic coherence (the logical flow and connectedness
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of speech, capturing symptoms such as derailment or tangentiality) and syntactic complexity (i.e., shorter sentences, reduced pronoun use; Corcoran et al., 2018).

Furthermore, despite its lack of inclusion in the diagnostic criteria for schizophrenia, cognitive impairment is recognized by the DSM-5 and most experts and clinicians as a characteristic symptom of the illness and a contributing and maintaining factor to vocational and functional impairment (Bowie et al., 2008; Bowie, Gorssman, Gupta, Oyewumi, & Harvey, 2014; American Psychiatric Association, 2013). A wealth of research has consistently identified cognitive impairments as ubiquitous and a defining feature of schizophrenia (Heinrichs & Zakzanis, 1998; Bowie & Harvey, 2006; Fioravanti, Bianchi, & Cinti, 2012). In addition to the apparent clinical and cognitive symptoms and their related functional impairments, other neuropsychological symptoms have been reliably identified in schizophrenia, particularly related to perceptual and visual processing deficits (Koychev, El-Deredy, & Deakin, 2011). For instance, deficits in visual backwards masking and inhibitory control over saccadic eye movements are well-replicated in the literature (Herzog, Roinishvili, Chkonia, & Brand, 2013; Munoz & Everling, 2004; Reilly et al., 2014; Radant et al., 2010).

The Prodromal Phase and First-Episode Psychosis

The aforementioned impairments do not spontaneously develop at the time of a diagnosis of schizophrenia; rather, they emerge in a developmental context, and are often present many years before the onset of psychotic symptoms or the communication of a diagnosis. Behavioural, emotional, and perceptual abnormalities, cognitive impairment, and disturbances in communication and sleep often precede the onset of psychosis (Larson, Walker, & Compton, 2010; Malla & Payne, 2005). Several different stages traditionally categorize the initial course of schizophrenia. For example, the prodrome phase of psychosis refers to the period of time where
a person experiences attenuated psychotic symptoms and the first signs of behaviour change before the onset of the illness. This stage, which is typically retroactively identified, is associated with a number of schizophrenia-like symptoms, including reduced attention, amotivation, sleep disturbances, suspiciousness, deterioration in functioning, social withdrawal, perceptual abnormalities, and anxiety (Yung & McGorry, 1996). The presence of prodromal symptoms such as thought interference, language disturbances, and visual distortions have been found to predict schizophrenia with a probability up to 91%; the absence of prodromal symptoms excluded schizophrenia with a probability of 96% (Klosterkotter et al., 2001). Meta-analytic evidence suggests that cognitive deficits are established even before the prodromal stage among individuals diagnosed with first-episode psychosis or who are at ultra-high risk for psychosis (Bora & Murray, 2014; Fusar-Poli et al., 2012; Aas et al., 2014). Social cognitive domains, including theory of mind, social perception, attributional bias, and emotion processing are also significantly impaired among individuals in the prodrome phase of psychosis (Lee, Hong, Shin, & Kwon, 2015). Related, subtle language disturbances, such as reductions in semantic coherence and syntactic complexity, are present among individuals at high risk for psychosis (Corcoran et al., 2018). For some, the prodromal phase is then followed by a first-episode of psychosis, which is often characterized by delusions, hallucinations, paranoia, thought disorders, and social impairment (Malla, Norman, Manchada, & Townsend, 2002).

Endophenotypic symptoms of schizophrenia, which refer to the not-easily-observable, genetically-linked characteristics of the illness (e.g., eye movement abnormalities), are also present in the prodromal and early stages of illness; visual-perceptual, visual and information processing, and language abnormalities have all been identified in schizophrenia (Keane, Cruz, Paterno, & Silverstein, 2018; Bodatsch, Klosterkotter, Muller, & Ruhrmann, 2013; Koethe et al.,
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2009; Haenschel et al., 2007). In particular, abnormalities in anti-saccadic eye movement (Ettinger et al., 2004; Kleineidam et al., 2019) and visual backward masking (Lee et al., 2008; Perez, Shafer, & Cadenhead, 2012) have been consistently recognized both in and preceding first-episode psychosis.

Although a first episode of psychosis may be indicative of the early stages of a schizophrenia-spectrum disorder, it may also be the result of another mental illness (e.g., bipolar disorder), a medical condition (e.g., brain injury, sleep deprivation), or alcohol or drug abuse; these alternatives must be ruled out in the diagnostic process for schizophrenia. As such, only a subset people who experience a first episode of psychosis go on to receive a diagnosis of schizophrenia (Henry et al. 2010). In one meta-analysis of 14 848 individuals with first-episode psychosis, only approximately 20% received a diagnosis of a schizophrenia-spectrum disorder (Fusar-Poli et al., 2016). In a first-episode treatment clinic, the similarities in symptom presentation often render it difficult to discern the origin of psychosis for each individual person. In particular, the high rate of substance use and abuse among individuals with psychosis and schizophrenia presents a challenge to clinicians attempting to determine if an episode of psychosis is more proximally related to drug and alcohol consumption (e.g., an induced psychosis), or if substance use is co-occurring with an underlying psychotic disorder.

Substance Use in Schizophrenia and Psychosis

Substance use is highly comorbid among individuals with schizophrenia and psychosis. According to the DSM-5, the lifetime prevalence of schizophrenia is approximately 0.3% - 0.7%, placing the global number of people diagnosed with schizophrenia between 23 and 54 million (American Psychiatric Association, 2013). Of these individuals, as many as half will meet criteria for a substance use disorder in their lifetime (Regier, 1990). The use of cannabis is
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especially common. Meta-analytic results place the lifetime rate of cannabis use disorders among those with schizophrenia as 27.1%, compared to 8% in the general population (Koskinen, Löhönen, Kopnen, Osohanni, & Miettunen, 2010). Prevalence is notably higher among individuals with first-episode psychosis (Schoeler et al., 2016; Caton, Samet, & Hasin, 2000), with 40-70% meeting criteria for a comorbid substance use disorder (Lambert et al., 2005; Ouellet-Plamondon, Abdel-Baki, Salvat, & Potvin, 2017), and 19-57% reporting actively using cannabis (Seddon et al., 2016; Oluwoye et al., 2017; Hadden, LeDrew, Hogan, & Thomas, 2016). Young people at ultra-high risk for psychosis, who may have brief intermittent psychotic symptoms or be at genetic risk for psychosis, are five times more likely to have a cannabis use disorder (Carney, Cotter, Firth, Bradshaw, & Yung, 2017), highlighting the need for further research at the early stages of illness.

Several theories have arisen as to why rates of cannabis use and abuse are elevated in this population, including: 1) that substance use arises secondarily to severe mental illness (e.g., self-medication hypothesis); 2) that substance use precedes, or in some cases has a causal effect on, the development of severe mental illness; 3) that both substance use and psychiatric illness have shared underlying genetic or psychosocial risk factors; or 4) there is a bi-directional relationship between substance use and psychiatric illness, each propagating and maintaining the other (Kolliakou et al., 2015; Thoma & Daum, 2013; Mueser, Drake, & Wallach, 1998). One of the most widespread theories is the self-medication hypothesis, which hypothesizes that people use substances to reduce particular symptoms of psychosis; a variant of this hypothesis focuses specifically on the alleviation of dysphoria (Gregg, Barrowclough, & Haddock, 2007; Mané et al., 2015). Positive feelings, coping with negative affect, and social activity are also consistently reported as reasons for cannabis use (Schofield et al., 2006; Kolliakou et al., 2015; Gill et al.,
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2013). Of particular importance to note is that many individuals with psychosis may have begun using cannabis to cope with prodromal symptoms prior to the onset of illness, or sought mood enhancement due to emerging amotivation, apathy, or depressive symptoms associated with psychotic illnesses (Khantzian, 1997; Gregg, Barrowclough, & Haddock, 2007). Thus, cannabis use may precede the observable onset of illness, but not necessarily the illness itself, contributing to diagnostic uncertainty. As many symptoms remain relatively stable throughout the chronic course of schizophrenia, motivations to use cannabis or other substances may continue to persist.

Cannabis-Induced Psychosis

High rates of cannabis use in a young population with emerging psychosis has directed attention towards cannabis-induced psychosis. The diagnostic criteria for substance-induced psychotic disorder require the presence of delusions and/or hallucinations developing during, or soon after, substance intoxication or withdrawal, and that these symptoms do not persist for a substantial period following substance abstinence (which, if persistent, would be evidence for an independent psychotic disorder; American Psychiatric Association, 2013). However, these criteria have been difficult to apply for several reasons. First, symptoms of cannabis-induced psychosis present similarly, or even indistinguishably, to a primary psychotic disorder (e.g., schizophrenia), especially during acute stages of illness when individuals are likely to be entering a psychiatric facility or intervention program (Fraser, Hides, Phillips, Proctor, & Lubman, 2012; Rubio et al., 2012; Starzer, Nordentoft, & Hjorthøj 2018). Given that many individuals with primary psychosis also use cannabis, it is not immediately evident whether use of the drug may be related to symptom onset, and, by extension, critical to symptom recovery. Second, cannabis use among those with primary psychosis often occurs in the prodromal stage, preceding the visible onset of illness, making temporality and causality difficult to discern.
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(Grewal & George, 2017; Rosenthal & Miner, 1997; Ksir & Hart, 2016). Third, given the high rates of cannabis abuse in this population, cessation of use for a period long enough to meet diagnostic criteria (i.e., 4 weeks) is often either undesirable or unattainable for the patient and exceedingly challenging to accurately monitor for the clinician (Fraser et al., 2012; Wilson, Szigeti, Kearney, & Clarke, 2018). Overall, psychotic symptoms appearing during periods of heavy drug use are not unique to either cannabis-induced or primary groups, rendering it difficult to reliably determine if symptoms are cannabis-induced or reflective of an underlying primary psychotic disorder, thus complicating the diagnostic process (Wilson et al., 2018).

Importance of Differentiating Cannabis-Induced and Primary Psychosis

The high rates of cannabis use among individuals with psychosis and the lack of diagnostic clarity surrounding cannabis use and psychotic symptom onset have led some researchers to propose that cannabis-induced psychosis is a precursor to schizophrenia (Arendt, Mortensen, Rosenberg, Pedersen, & Waltoft, 2008). Research investigating this theory has explored rates of conversion from diagnoses of cannabis-induced psychosis to schizophrenia. Findings have demonstrated that among individuals with a diagnosis of cannabis-induced psychosis, the risk to receive a schizophrenia-spectrum diagnosis in an 8-year period was 46% (Niemi-Pynttäri et al., 2013); similar rates were found by both Starzer and colleagues (47%; 2018) and Arendt and colleagues (45% within 3 years; 2005). However, another study found only a 17.3% rate of conversion from a diagnosis of substance-induced psychosis to schizophrenia in a 15-year period (Alderson et al., 2017). From these results, we would expect that over half of individuals diagnosed with cannabis-induced psychosis do not go on to develop a schizophrenia-spectrum disorder, highlighting the prevalence of cannabis-induced psychosis and the importance of distinguishing it from primary psychosis.
In the early stages of psychosis, correct diagnosis and timely treatment is critical to symptomatic and functional recovery (Seddon et al., 2016). Further, the decision to initiate antipsychotic treatment hinges on determining the primacy of a psychotic disorder. Inaccurate diagnoses may lead to unnecessary use of antipsychotic medication, place individuals at higher risk of treatment failure, or result in stigmatization and adverse social and vocational outcomes (Caton, Samet, & Hasin, 2000; Fraser et al., 2012). Fortunately, the importance of differentiating between cannabis-induced and primary psychoses for proper diagnosis, intervention, and treatment has spurred research efforts to identify unique diagnostic features of the illnesses.

**Contemporary Efforts to Differentiate Cannabis-Induced and Primary Psychosis**

Preliminary research has reported some relatively consistent differences between cannabis-induced and primary groups, initiating further efforts to reliability differentiate these diagnoses. Despite first-episode psychosis groups being particularly relevant to this debate due to high rates of cannabis use and potential lack of diagnostic clarity due to shorter illness duration, research specific to first-episode psychosis is sparse. A 2018 review by Wilson and colleagues identified only six studies examining differences between first-episode primary psychotic disorders with comorbid substance abuse and substance-induced psychotic disorders. Of these six studies, only two focused exclusively on cannabis-induced psychosis (Wilson et al., 2018). The main findings in both this review and the literature as a whole are summarized below. Due to the paucity of research in this area, findings from studies focusing on both substance-induced psychosis generally and cannabis-induced psychosis specifically are explored.

**Clinical Symptoms**

Psychotic and mood symptoms are frequent targets for exploring differences between these groups, but have been the subject of many mixed findings. The review by Wilson and colleagues
(2018) found evidence that individuals with substance-induced psychotic disorders have fewer positive and negative symptom scores and more anxiety. However, a separate meta-analysis found more positive symptoms among substance users (Large, Mullin, Gupta, Harris, & Nielssen, 2014). More severe symptoms of depression were found in the cannabis-induced group, though this finding did not extend to the substance-induced group as a whole (Wilson et al., 2018). Additional findings from individual studies within the review suggest that those with substance-induced psychosis are more likely to have a neurotic profile (i.e., interpersonal sensitivity, anxiety, and depression; Rubio et al., 2012) and more severe hostility (Fraser et al., 2012). Social anxiety and social phobia were both also identified as potential predictors in a separate review, which found that 20% of patients with cannabis-induced psychosis experienced social phobia compared to just 3.8% of those with primary psychosis (Grewal & George, 2017). Other explorations of cannabis-induced psychosis have found that derealization, depersonalization, and sensory disturbances were more frequent in cannabis-induced psychosis compared to acute schizophrenia (Núñez & Gurpegui, 2002), as were visual hallucinations (Caton et al., 2005; Grewal & George, 2017).

**Premorbid Intellectual Functioning and Adjustment**

In line with findings demonstrating that cognitive impairment in schizophrenia begins prior to the onset of illness (Woodberry, Guiliano, & Seidman, 2008), some researchers have investigated premorbid intellectual functioning across substance-induced and primary psychosis. Studies have also explored premorbid adjustment, which refers to one’s level of psychosocial functioning and developmental achievement before illness onset, in domains such as school and interpersonal relationships (Cannon-Spoor, Potkin, & Wyatt, 1982). Despite prior research identifying better premorbid intellectual functioning and adjustment among individuals
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diagnosed with substance-induced psychosis compared to primary psychosis (Sevy et al., 2001; Arndt, Tyrrell, Flaum, & Andreasen, 1992; Buckley, Thompson, Way, & Meltzer, 1994), the review by Wilson and colleagues (2018) found no difference in level of premorbid adjustment and functioning between those with substance-induced psychosis and primary psychosis.

Illness Insight

Lack of insight into illness has long been identified as a feature of schizophrenia. Insight into one’s illness includes a person’s recognition that they have a mental illness, that their symptoms are pathological, that they need treatment, and that the source of their symptoms (e.g., delusions, hallucinations) is an illness (Beck, Baruch, Balter, Steer, & Warman, 2004). Impaired insight plays a role in the maintenance of unusual beliefs surrounding positive symptoms, as well as the resistance to feedback and alternative explanations for unusual experiences (Beck et al., 2004). Illness insight has been suggested to be greater among individuals with substance-induced psychoses compared to those with primary psychoses. Overall, Wilson and colleagues’ review (2018) found evidence that individuals with substance-induced psychotic disorders have more insight into their illness (Fraser et al., 2012; Caton et al., 2005). In a separate review, Grewal and George (2017) identified insight and awareness of one’s condition as one of the strongest distinguishing factors between groups, with individuals with cannabis-induced psychosis having greater ability to identify their symptoms as resulting from a mental disorder or cannabis use.

Substance Use

Higher rates of substance use in the cannabis-induced group are consistent across the literature. Findings suggest that those with substance-induced psychosis are more likely to have a drug dependency diagnoses, higher rates of substance use and abuse, and current cannabis dependence (Caton, 2005; Fraser et al., 2012). Poly-substance use has been identified as one of
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the strongest predictors of developing a substance-induced psychotic disorder (Wilson et al. 2018).

**Trauma**

Only one study thus far has explored trauma history as a potential predictor of *cannabis-induced* psychosis, with findings suggesting that individuals with substance-induced psychosis are up to 23 time more likely to have a history of trauma compared to individuals with a primary psychotic disorder (Fraser et al., 2012). Given that both substance use and trauma history are risk factors for psychotic symptoms, this may represent a unique vulnerability factor for *cannabis-induced* psychosis that warrants further exploration (Fraser et al., 2012). These findings, however, are encompassing of any form of substance-induced psychosis, rather than specific to *cannabis-induced* psychosis.

**Evidence for Novel Neuropsychological Approaches to Differentiating Cannabis-Induced and Primary Psychosis**

There is a scarcity of research examining potential differences between substance-induced and *primary* psychosis, limited studies focusing on first-episode psychosis, and even fewer exploring *cannabis-induced* psychosis specifically. Differential research thus far has been relatively inconsistent and limited to patient history and symptom presentation with an overreliance on self-report and clinician interviews. The domains assessed have produced variable findings, are often subjective or retrospective, and some may vary greatly over time and across individuals with the same diagnosis. There is a clear need for further research that addresses these shortcomings. Surprisingly, very limited research has attempted to utilize any of the core neuropsychological characteristics of schizophrenia as a means of differentiating these disorders. Only a few studies have explored either the use of cognitive assessments, eye-tracking,
or linguistic analysis to identify biomarkers or neuropsychological soft signs to differentiate cannabis-induced from primary groups in first-episode psychosis, and no study to date has analyzed multiple neuropsychological methods in combination. Furthermore, few studies have explored cannabis-induced psychosis specifically; findings often discuss substance-induced psychosis as a whole. Given the abundance of research identifying neurocognitive deficits and linguistic and eye-movement abnormalities in schizophrenia, it follows that these variables may be a promising avenue in the differentiation of primary psychotic disorders from induced psychoses.

Cognition

Cognitive impairments are a core feature of schizophrenia, often presenting before a first psychotic episode (Bowie & Harvey, 2005). Deficits in attention, verbal fluency, working and verbal memory, processing speed, and executive functioning are pervasive across the illness (Bowie & Harvey, 2005). Since cannabis-induced psychosis is an induced rather than a primary psychotic disorder, it may not be characterized by the same degree of premorbid cognitive impairment that is present in schizophrenia and associated with the developmental and chronic course of the illness. Therefore, the presence, or lack thereof, of cognitive deficits typical of schizophrenia offers useful diagnostic information. Of the limited literature comparing cognitive performance in substance-induced psychosis with schizophrenia, evidence points to less severe deficits in the substance-induced group (Fitzgerald et al., 2004; Harris et al., 2005). A study by Fitzgerald and colleagues (2004) comparing neuropsychological deficits in first-episode psychosis found that those with a primary psychosis experienced global impairment in most cognitive domains, whereas those with substance-induced psychosis, though still impaired, exhibited less severe deficits. This moderate impairment may be associated with the use of
substances, though further research is necessary to parse apart the independent effects of cannabis use and psychotic illness on cognition.

**Eye Movements**

Eye-tracking abnormalities are among the most reliably identified features of schizophrenia. Differences in smooth pursuit, saccadic control, visual scan paths, and fixation dispersal have been consistently reported (Benson et al., 2012). The pro-saccade and anti-saccade task, which requires participants to both suppress the automatic visual response to look at a target (pro-saccade) and actively look away from the target (anti-saccade), is significantly impaired in schizophrenia (Munoz & Everling, 2004). Performance on this task is related to executive functioning, attentional control, response monitoring, and inhibition (Thakkar, Schall, Logan, & Park, 2015; Bansal et al., 2019). Specifically, the inability to inhibit pro-saccadic eye movements is thought to be related to impairment of the dorsolateral prefrontal cortex (Munoz & Everling, 2004). Compared to healthy controls, individuals with schizophrenia show significantly greater error rates and prolonged latencies to correct responses (Mazhari et al., 2011). These abnormalities, proposed as an endophenotype for schizophrenia, are present in those at ultra-high risk of psychosis and appear to be stable across the course of illness, independent of medication use (van Tricht et al., 2010; Benson et al., 2012). They are hypothesized to be related to deficits in visual processing and inhibitory control present in schizophrenia (Caldani et al., 2017).

Eye-tracking research exploring the effects of cannabis on eye movements have found that long-term cannabis users also show latency in prosaccade and anti-saccade tasks, which are indicative of poorer temporal processing and visuo-spatial memory deficits (Huestegge, Radach, Kunert & Heller, 2002; Huestegge, Radach, & Kuner, 2009). No research to date has explored pro- and anti-saccadic eye-movements in *cannabis-induced* psychosis, nor directly compared
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*cannabis-induced* or primary psychosis. However, one study exploring visual scan paths in *cannabis-induced* psychosis and schizophrenia found that both groups made fewer saccades compared to healthy controls (Benson et al., 2007). A more in-depth exploration of pro- and anti-saccadic behaviour specifically would further clarify whether differences exist between this groups. Overall, findings point to some shared abnormalities between *cannabis-induced* and schizophrenia groups, but an existing potential for differentiation, warranting further research.

**Speech and Language**

Disorganized speech, semantic incoherence, and abnormalities in language areas of the brain are consistent findings in schizophrenia (Marini et al., 2008). Individuals with schizophrenia typically display flattened speech, verbosity, reduced use of possessive pronouns, derailments, and other disordered language (Marini et al., 2008; Corcoran et al., 2018). In particular, individuals with psychosis show reduced semantic coherence and syntactic complexity, and greater variance in semantic coherence across speech compared to healthy individuals (Corcoran et al., 2018). As a result, linguistic analyses are successful in discriminating speech in psychosis from healthy speech. Using a machine-learning automated speech classifier, Corcoran and colleagues (2018) were able to distinguish and predict psychosis, finding that analyzing speech characteristics such as semantic coherence accurately predicted psychosis onset during the prodromal stages and had 72% accuracy in differentiating the speech of first-episode psychosis patients from healthy controls. Related research has found that semantic coherence and syntactic complexity predicted the development of psychosis in high-risk youths with 100% accuracy, albeit in a small sample (Bedi et al., 2015).

Cannabis use alone has not been found to produce any such speech abnormalities. Of the few studies on cannabis use and speech, the only distinct features identified were increased latency
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and decreased quantity of speech, although these were suggested to result from short-term memory impairments and difficulty remembering aspects of the conversation (Higgens & Stitzer, 1986; Weil & Zinberg, 1969). Therefore, it is plausible that individuals with cannabis-induced psychosis perform similarly to healthy controls on a speech task or display abnormalities at a lesser severity than those with a primary psychotic disorder with or without cannabis comorbidity.

**Backward Masking**

Visual processing deficits in schizophrenia have been attributed to dysfunction in low-level sensory processes, such as in the magnocellular visual pathway. The magnocellular visual pathway is one of the major pathways of the visual system (along with the parvocellular pathway), responsible for carrying information to the primary visual cortex (Martínez et al., 2008). Unlike the parvocellular pathway, it is sensitive to low levels of luminance contrast; as such, at low contrast levels, it is the main system engaged with conveying visual information to the primary visual cortex (Martínez et al., 2008). Research supporting the hypothesis that magnocellular dysfunction is associated with visual professing deficits has found that individuals with schizophrenia show reduced activation in multiple regions of the occipital, parietal, and temporal lobes, which are suggestive of sensory processing deficits related to impaired functioning of the magnocellular pathway (Martínez et al., 2008). Backward masking tasks are commonly used to assess deficits in visual processing, information processing, and attention in individuals with schizophrenia (Herzog, Roinishvili, Chkonia, & Brand, 2013). In these tasks, a target is presented to a participant and quickly covered with a mask, impairing one’s ability to identify the target. Although both clinical participants and healthy controls show impaired task performance following masking, participants with schizophrenia exhibit much more significant
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deficits (Chkonia et al., 2010). Previous research has identified a reliable masking deficit in individuals with schizophrenia compared to healthy controls, such that they require a longer interval between the target and masking stimulus which has been suggestive of information processing deficits (Saccuzzo & Schubert, 1981). Furthermore, research has identified visual masking as a potential endophenotype for schizophrenia, finding that masking deficits are stable over time and intermediate for immediate relatives of individuals with schizophrenia (Chkonia et al., 2010). No research to date has explored magnocellular or visual backward masking deficits in cannabis-induced psychosis.

The Present Study

Objectives

The primary aim of the present study was to use a novel neuropsychological approach to assessing whether individuals diagnosed with cannabis-induced or primary psychosis significantly differ in factors typically impaired in schizophrenia but which may be relatively intact in cannabis use disorders, namely cognition, eye movements, and/or use and patterns of speech, and if these variables can be used as differentiating biomarkers. The secondary aim of this study was to explore previously assessed symptoms in the literature that have a strong evidence base for potential differentiating ability; secondary variables analyzed included premorbid adjustment, illness insight, and clinical symptoms. The final goal of the present study was to assess supplementary variables, which are those variables that have appeared in the literature but have lacked strong evidence to support their use as differentiating variables, and thus require further exploration and clarification. Supplemental variables included social anxiety symptoms, trauma history, and premorbid intelligence. If participants can be reliably
distinguished through these means, it would allow for earlier and more accurate diagnoses of cannabis-induced and cannabis-comorbid psychosis.

There are two overarching objectives for this study:

1) Characterize the impairment of individuals with cannabis-induced psychosis compared to primary/induced psychosis on measures assessing cognition, speech, and visual processing, clinician-rated measures of clinical symptoms and premorbid adjustment, and self-report measures of illness insight, social anxiety, trauma, and substance use.

2) Assess whether these variables can successfully differentiate between cannabis-induced and primary psychosis and predict group membership.

Hypotheses

The following are hypothesized:

1) **Primary hypotheses:**
   
   A. The cannabis-induced group will perform significantly better than the primary psychosis group on pro- and anti-saccade tasks, showing better attentional shifting and more inhibitory control over eye movements.
   
   B. The cannabis-induced group will demonstrate significantly greater semantic coherence and syntactic complexity of speech compared to the primary psychosis group.
   
   C. The cannabis-induced group will perform significantly better on visual backward masking tasks compared to the primary psychosis group.
D. The cannabis-induced group will show significantly fewer cognitive impairments in working memory and processing speed compared to the primary psychosis group.

2) Secondary hypotheses:
   A. The cannabis-induced group will show significantly higher levels of premorbid adjustment than the primary psychosis group.
   B. The cannabis-induced group will show significantly greater insight into their illness than the primary psychosis group.
   C. The cannabis-induced group will have significantly less severe positive and negative symptoms, but significantly more severe affective symptoms (e.g., depression, anxiety) than the primary psychosis group.

3) Supplemental hypotheses:
   A. The cannabis-induced group will show significantly higher premorbid intellectual functioning than the primary psychosis group.
   B. The cannabis-induced group will report significantly more substance use (including cannabis, alcohol, and other substances) than the primary psychosis group.
   C. The cannabis-induced group will report significantly more traumatic life experiences than the primary psychosis group.
Chapter 2  
Methods  

Study Design and Participants  

Participants were recruited from the Early Psychosis Intervention Program at Hotel Dieu Hospital in Kingston, Ontario. Participants had to be between the ages of 16 and 40, which captures the typical age of onset for psychosis, and within the first five years of psychosis to be considered for the present study. Participants had to be able to read and speak English. Based on the treating psychiatrist’s final diagnosis, participants were grouped into two groups: cannabis-induced psychosis or a primary psychotic disorder (primary psychosis). The process of diagnosis typically occurs within the first three months of entry to the program, and diagnoses may be provisional in nature during the first-episode stage as symptoms emerge and fluctuate. Weekly team meetings with case conferences are held to have interdisciplinary involvement in the formulation of diagnosis. Therefore, some participants were tested before their diagnosis had been determined and were retroactively placed into either group. A power analysis was used to determine the appropriate sample size needed to achieve a power level of .80 in a one-way ANOVA with a moderate effect size of .50 (Faul, Erdfelder, Buchner, & Lang, 2009). A total sample size of 34 was required for the two groups (cannabis-induced and primary psychosis), equalling to 17 participants per group. The present study represents the pilot stage of a longer-term project.

All participants completed the following: a demographics interview; a psychotic symptom interview; cognitive tasks; two computerized tasks; a speech role-play task; an assessment of premorbid functioning; and self-report questionnaires regarding anxiety symptoms, insight, trauma history, and drug use. Computer tasks were run on a 15.6” Acer laptop. The tasks were
programmed and run using Matlab presented with the Psychophysics Toolbox. Internal reliability statistics and bivariate correlations among study variables are presented in Appendix B and C, respectively.

**Demographics Interview.**

Demographic information was collected with a structured interview conducted by the experimenter. Information of interest included age, sex, self-identified ethnicity, native language, location of birth and residence, marital status, living circumstances, educational and occupational history, clinical diagnostic history, smoking history (tobacco and cannabis), and current medications. Demographics were collected as a means of characterizing the sample and for consideration of covariates as necessary.

**Primary Outcome Measures**

**Pro- and Anti-Saccadic Eye Movements**

Participants completed a reaction time-based computerized task to assess their eye movements. The pro- and anti-saccade task (adapted from Roberts, Hager, & Heron, 1994 and Friedman et al., 2008) measures participants’ voluntary control and inhibition of their eye movements. Pro-saccades assess the automatic response (to look at a stimulus that appears), whereas anti-saccades assess voluntary control, as subjects must inhibit the automatic response to look at a visual cue, and instead actively look away from the visual cue to the target on the opposite side of the screen. This task uses reaction time responses as a proxy of eye movement, where participants are required to react to images on a screen that appear rapidly, and in such a way that if a participant does not immediately look at an image (pro-saccade) or suppress their automatic response to look at an image (anti-saccade), they will miss the target cue and thus be unable to correctly respond to the task using the arrow keys.
On the pro-saccade task, each trial begins with a central fixation point appearing in the middle of the screen for a variable amount of time (between 1500 and 3500ms in 250ms intervals). A visual cue in the form of a green square then appears on either the left or the right side of the screen for 150ms. This cue is then replaced by a target arrow which points either left, up, or right. The direction of the arrow was randomized across all trials. The target arrow remains on the screen for 175ms. It is then masked by a grey box, which remains on screen until participants respond about the direction of the arrow using the keyboard arrow keys. Following the participant response, a new trial begins.

The anti-saccade task functions similarly to the pro-saccade task, except the visual cue flashed on the screen is a yellow square, and the presentation of the target arrow is on the opposite side of the screen from the cue. As such, participants are required to ignore the yellow square and direct their attention to the opposite side of the screen in order to see the target arrow.

The task consisted of two test blocks (18 trials each) and two practice blocks (90 trials each). For all participants, the pro-saccade practice and test blocks were presented first, followed by the anti-saccade practice and test blocks. Six different trial types (15 trials per type) were randomly presented in the test blocks: 2 (target locations: right or left) x 3 (target arrow direction: left, up, or right). Variables recorded included keypress reaction time and response accuracy. Reaction time was measured in seconds and averaged across all trials to create a mean score, and accuracy was computed as percent of trials correct, and thus scores range from 0 – 100% with higher accuracy indicating more correct responses and thus greater voluntary control and inhibition of eye movements. This task takes approximately 15 minutes to complete.
Interpersonal Competence and Speech

The Social Skills Performance Assessment (SSPA; Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001) consists of three standardized social role-plays, each requiring the participant to initiate and maintain conversation with the examiner. The SSPA has a high test-retest reliability (.92) and intraclass correlation coefficient (.91). In Scene 1 (“Friend”; 1 minute in length), the participant was asked to discuss making plans to get together with a friend. In Scene 2 (“New Neighbour”; 3 minutes in length), the participant is asked to greet a new neighbour. In Scene 3 (“Landlord”; 3 minutes in length), the participant is asked to call a landlord to negotiate the fixing of a leak that has gone unrepaid. The interviewer reciprocates the conversation as initiated by the participant using prescribed prompts. The interview is audio-recorded and scored. Scene 1, which is typically used as a practice session, does not have predetermined scoring criteria and thus was not scored. Scenes 2 and 3 were each scored on a behaviourally anchored rating scale from 1 (low) to 5 (high) in the following categories: Interest/Disinterest (motivation and willingness to engage in the interaction), Fluency (overall flow of conversation as determined by speech mannerisms), Clarity (ability and willingness to express self clearly and directly), Focus (ability to concentrate on and track the content of the roleplay), Social Appropriateness (reflecting participant’s adequate conduct during the scene). Additional scene-specific scoring criteria for the New Neighbour scene includes: Overall Conversation (comprehensive rating of participant’s ability to meet the new neighbour). Additional scoring criteria for the Landlord scene includes: Negotiation Ability (willingness and ability to generate solutions and make compromises), Submissive-Persistent (the extent to which the participant is able or willing to stick firmly to their goal of reaching a resolution), and Overall Argument (a comprehensive rating of the subject’s interaction with the landlord). Scores for the
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New Neighbour scene range from 0 to 30 and for the Landlord scene range from 0 to 40. Accuracy in interpersonal competence was defined as the percent of the maximum score achieved, ranging from 0 – 100%, with higher scores indicating better interpersonal competence.

The SSPA audio files were then transcribed by undergraduate research assistants to support computerized linguistic analysis, which explored semantic coherence and language complexity across each scene. Novel computational methods were used to aid in the identification of linguistic biomarkers that are indicative of the presence and severity of cognitive and processing impairments in psychological conditions such as psychosis. Mean scores for semantic coherence were calculated for each scene, and an overall syntactic complexity score was calculated across all three scenes. An overall score for semantic coherence was not utilized due to previous research findings demonstrating that semantic coherence differs significantly depending on the level of ambiguity in the SSPA scenes, with the landlord scene being the least ambiguous and the new neighbour scene being the most ambiguous (Woolridge et al., 2019). Coherence across varying levels of ambiguity was also found to differ depending on an individual’s diagnosis, with individuals with schizophrenia showing less coherence than those with bipolar disorder or healthy controls (Woolridge et al., 2019).

Backward Masking

Visual backward masking impairment was measured with an object substitution masking (OSM) task developed by Goodhew, Boal, and Edwards (2014). In this task, four “pedestals” (homogenous grey squares) appeared surrounding a central fixation point. A letter C would then appear in each square, with the gap in the C located on either the left or the right (C facing either forward or backward). In one of the squares, the C is surrounded by four small dots (the mask), one in each corner of the square. This is the target array. In OSM tasks, perception of a target (C)
is impaired by a mask (dots) that does not overlap or share common contours with the target (Goodhew et al. 2014). Masking magnitude is determined by looking at the difference in accuracy between trials where the mask remains after a target disappears (delayed mask offset condition), and control trials where the target and mask disappear simultaneously (simultaneous mask offset condition). As described by Goodhew, Boal, and Edwards (2014), “masking occurs when the target array and trailing mask are mistaken for a single object continuing through time, resulting in the representation of the object for that location being updated to reflect the longer trailing mask, at the expense of the target.”

Magnocellular pathway impairment was examined using two pedestal conditions: steady-pedestal and pulsed-pedestal. In both pedestal conditions, the pedestal (grey square on a black background) cause a rapid increase in luminance, which activates magnocellular cells that are sensitive to changes in luminance. In the pulsed-pedestal condition, the pedestal appears at the same time as the target and mask stimuli, which saturates object-selective magnocellular response, such that the visual system treats the mask and target as belonging to the same object (Goodhew, Boal, & Edwards, 2014). In the steady-pedestal condition, the pedestal appears in advance of the target and mask array, which provides the magnocellular cells with enough time to process the pedestal, diminish response, and be available to process the target and delayed mask (Goodhew, Boal, & Edwards, 2014).

Based on the conditions described above, this task was configured in a 2 (condition: steady-pedestal vs. pulsed-pedestal) x 2 (mask duration: simultaneous offset (0ms) vs. delayed offset (160ms)) model. The task was presented in two blocks, separated by pedestal condition. Participants were randomized to receive either the steady-pedestal or pulsed-pedestal condition first. Each trial began with a white fixation cross displayed on the screen for 1000ms. In the
steady-pedestal condition, the four pedestals appear alongside the fixation cross. Then target array (C and four dots) is then presented for 53ms. On delayed mask offset trials, the four-dot mask remains on the screen for an additional 160ms. Blank pedestals then remain on the screen until participants enter a response. Participants were told to identify the location of the gap in the C as either on the left or on the right using the corresponding arrow keys on the keyboard. Following a response, the screen remains blank for 1000ms before the onset of a new trial. The location of the gap in the C, the location of the target, and the mask duration were randomly assigned for each trial, though an equal number of trials per type (gap on left vs. right, location of target, 0ms vs. 160ms mask duration) were maintained for each block. Participants completed 128 trials per pedestal condition and received a break between the blocks. The first five trials from each block were used as practice trials and not included in the analysis. Dependent variables included the percent of trials correct for each of the steady- and pulsed-pedestal conditions at either the 0ms or 160ms trailing mask duration. This task takes approximately 15 minutes to complete.

Cognition

Participants completed two cognitive tasks, measuring attention, processing speed and working memory. Completion of both tasks takes approximately 10 minutes.

*Digit Symbol Coding (Keefe et al., 2004).* The Digit Symbol Coding test is a subtest of the Brief Assessment of Cognition in Schizophrenia (BACS) instrument. It is a measure of attention and information processing speed and takes around 2-3 minutes to complete. Participants are shown a key with symbols which correspond to the numbers 1-9 and must correctly match a sequence of random symbols to their corresponding number by writing the number in a blank space below the symbol. Participants are told to complete the task as quickly as possible and are
stopped after an allotted time of 90 seconds. Composite scores on the BACS are highly correlated with standard battery composite scores (Keefe et al., 2004). T-scores were calculated using MATRICS Consensus Cognitive Battery software (Nuechterlein et al., 2008) and accounted for each participant’s age and years of education.

**Alpha Span Test (Craik, Bialystok, Gillingham, & Stuss, 2018).** The alpha span test is a brief test of verbal working memory. In this test, short lists of words are read aloud to a participant, and the participant is required to mentally reorder the words and repeat them back in alphabetical order. A participant’s ‘alpha span’ is the longest list of words that they are able to recall in the correct order. This test also provides a second scoring method, ‘alpha score’, in which points are awarded for partially correct answers, allowing for further specificity in scoring and assessing deficits in working memory, especially among similarly performing participants (Craik et al., 2018). In calculating the alpha score, points are awarded for correctly ordered pairs (two correct words in a row) and correct first or last words (regardless of if they are paired). Participants’ total alpha score was analyzed in the present study. Further details on scoring and administration can be found in the original paper by Craik and colleagues (2018).

**Secondary Outcome Measures**

**Premorbid Adjustment**

The Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982) is a semi-structured interview measuring premorbid functioning up until a participants’ first experience of psychosis. The PAS assesses 5 domains of functioning: sociability and withdrawal; peer relationships; scholastic performance; adaptation to school; and social-sexual aspects of life. The PAS considers responses over 4 life periods: childhood (age 6 to 11), early adolescence (age 12 to 15), late adolescence (17 to 18), and adulthood (19 and older). Social-sexual aspects of life are
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not assessed in the childhood portion of the interview. The PAS is administered for life periods up to 1 year before the onset of psychosis. For example, if a participant experienced their first symptoms of psychosis at age 16, then only the childhood and early adolescent sections would be administered. If a participant had symptom onset at age 18, then the childhood, early adolescent, and late adolescent sections would be administered, although the late adolescent section would only consider experiences at age 17.

Each domain is scored on a 0-6 rating scale, with higher scores indicating poorer adjustment. Ratings for each domain in a certain life period are summed and divided by the total possible score. For example, the total score in the early adolescence section is 30 (maximum of 6 points for each of the 5 domains of functioning). If a participant’s scores in that domain summed to 18, their total score divided by their possible score would be .60. An overall score for the whole scale was then calculated by averaging the subscale scores for all of the completed subscales. The average was taken to avoid biased scores that would occur if a participant had a younger age of onset and thus only completed a few life periods of the interview. The overall score was analyzed in the present study. This interview is typically completed in 15-25 minutes.

Illness Insight

Insight into one’s illness was assessed using the Beck Cognitive Insight Scale (BCIS; Beck, Baruch, Balter, Steer, & Warman, 2004), a 15-item self-report scale designed to evaluate patients’ cognitive insight, with subscales measuring self-reflectiveness (objectivity, reflectiveness, openness to feedback) and self-certainty (certainty about being right, jumping to conclusions, resistance to correction; Beck et al., 2004). Participants are asked to rate how much they agree with each statement on a 4-point scale that ranges from 0 (Do not agree at all) to 3 (Agree completely). The BCIS demonstrates good convergent, discriminant, and construct
validity, and is significantly correlated with the Scale to Assess Unawareness of Mental Disorder (Beck et al., 2004). The BCIS is able to differentiate between inpatients with and without psychotic diagnoses, and change scores on the BCIS have been found to be associated with changes in positive and negative symptoms (Beck et al., 2004).

Scores on each of the two subscales were summed. A composite index was then calculated by subtracting the self-certainty score from the self-reflectiveness score, meant to reflect the fact that participants’ certainty about beliefs may affect their willingness to be open and reflective (Beck et al., 2004). A composite score (difference score) of 10 or greater is indicative of good illness insight (Beck et al., 2004). The composite score was analyzed in the present study.

Clinical Symptoms

The Brief Psychiatric Rating Scale (BPRS; Overall, Hollister, & Pichot, 1967), an 18-item semi-structured interview of psychotic symptoms, was used to measure the clinical symptoms. Symptoms are rated on a 7-point Likert scale assessing frequency and severity. Factor analyses have produced a consistent five-factor solution assessing the following domains: Affect (anxiety, depression, guilt, somatic), Positive Symptoms (unusual thought content, conceptual disorganization, hallucinations, grandiosity), Negative Symptoms (blunted affect, emotional withdrawal, motor retardation), Resistance (hostility, uncooperativeness, suspiciousness), and Activation (excitement, tension, mannerisms-posturing; Shafer, 2005). Mean item scores for each domain are reported, with higher scores indicating higher severity of symptoms. This interview is typically completed in 15-20 minutes.
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Supplementary Measures

Premorbid Intellectual Functioning

The Reading Subtest of the Wide-Range Achievement Test – 3rd Edition (WRAT3; Wilkinson, 1993) was administered to attain an estimate of participants’ premorbid intellectual functioning. This 2-3 minute test requires participants to read a series of increasingly challenging words out loud and assesses their ability to pronounce these words, which is a skill that has been found to be relatively preserved in schizophrenia (Franzen, Burgess, & Smith-Seemiller, 1997). T-scores were computed for each participant based on the number of correct words pronounced.

Alcohol Use

The Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, Monteiro, & World Healthy Organization, 2001) is a 10-item self-report questionnaire assessing the amount and frequency of alcohol consumption, alcohol dependence, and problems caused by alcohol. Items are assessed on a 5-point scale, with higher scores indicative of more serious alcohol-related problems. The AUDIT has been validated across genders and in a wide variety of ethnic groups (Babor et al., 2001). Scores on each item are summed to produce a total score.

Cannabis Use

The Cannabis Use Disorder Identification Test - Revised (CUDIT-R; Adamson et al., 2010) is an 8-item self-report screening tool designed to assess cannabis use and misuse. Items are assessed on a 5-point scale, with scores of 8 or more indicative of hazardous cannabis use. The CUDIT-R has high test-retest reliability ($r = .87$), and discriminant and predictive validity (Adamson et al., 2010). Scores on each item are summed to produce a total score.
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Substance Use

The NIDA Substance Use Checklist (National Institute on Drug Abuse, 2010) assesses the frequency of use of other drug types in a three-month period. Included on this checklist are cocaine, prescription stimulants, methamphetamine, sedatives, street opioids, and prescription opioids. Drug types are each rated on a 5-point scale ranging from Never to Daily/Almost Daily use. Scores on each item are summed to produce a total score.

Social Anxiety

The Liebowitz Social Anxiety Scale – Self-Report (LSAS-SR; Liebowitz, 1987) is a 24-item self-report instrument designed to measure social anxiety using two subscales: performance anxiety (e.g., eating or drinking in public, working in front of others) and social interactions (e.g., meeting new people, speaking with authority figures). The LSAS-SR assesses both fear and avoidance of the social situation presented in each item. As such, social fear and social avoidance subscales can be calculated for the scale. Fear is rated on a 4-point scale from 0 (no fear) to 3 (severe fear). Avoidance is rated on a 4-point scale based on the percentage of time the situation is avoided, as follows: 0 = never; 1 = occasionally (10%); 2 = often (33-67%); 3 = usually (67-100%; Liebowitz et al., 1987). The self-report version of the LSAS shows very little difference to the clinician-delivered version, and shows similarly high internal consistency, subscale intercorrelations, and convergent and discriminant validity (Fresco et al., 2001). An overall score was calculated by summing scores from both the fear and avoidance subscales across all items.

Trauma

The Brief Trauma Questionnaire – Revised (BTQ-R; Schnurr, Vielhauer, Weathers, & Findler, 1999) is a 13-item self-report questionnaire assessing lifetime traumatic exposure
according to Criterion A of the Post-Traumatic Stress Disorder diagnostic criteria in the DSM-5. The questionnaire was be used to determine the types of traumatic events an individual has experienced, with each event being score positively if it has happened to the respondent. The measure has been revised for the present study to include items regarding stigma and prejudice, disruptions to home life, and unplanned loss or termination of pregnancy. Follow-up questions were added to assess if participants were distressed by the event at the time, as well as if they are still currently bothered by the event. The original BTQ has adequate interrater reliability (K = .74-100) and is highly correlated with The Clinician-Administered PTSD Scale and lifetime PTSD severity scores ($r = .96$ and $.99$, respectively). Participants’ number of traumatic events experienced was reported in the present study.

**Procedure**

Participants completed the study either at the Cognition in Psychological Disorders Laboratory at Queen’s University or at the Heads Up! Early Psychosis Intervention Program at Hotel Dieu Hospital or Belleville General Hospital. The study was completed in one session and took between 1.5 and 2.5 hours to complete. Written informed consent was obtained from all participants before beginning the study. Following consent, participants took part in semi-structured interviews collecting information about demographics and their psychiatric symptoms. Participants then completed the SSPA, cognitive tasks, and computer tasks (pro- and anti-saccade and backwards masking). They were then provided with the self-report questionnaires to complete independently. Finally, participants took part in a semi-structured interview related to their premorbid functioning. An oral debriefing by the experimenter occurred immediately following study completion. Compensation of $50 per participant was offered for the time involved. Participants also had the option to have a clinical report prepared based on their
involvement in the study that would then be shared with their treatment team and used to guide future case management meetings.

Data Analysis

Chi-square analyses were conducted on categorical descriptive characteristics (sex, ethnicity, highest level of education achieved, and marital status) to assess for differences between groups. Group differences in age and premorbid intellectual functioning were assessed using independent samples t-tests.

Latent semantic analysis (LSA) was used to assess the semantic coherence of the transcribed SSPA interviews, producing a mean score per scene for each participant. A 2 (group: cannabis-induced vs. primary psychosis) x 3 (scene: friend, neighbour, landlord) mixed repeated-measures analysis of variance (ANOVA) was used to assess whether significant differences exist between the semantic coherence of the groups across the three different SSPA scenes. Individual scenes were then analyzed using one-way ANOVAs to explore whether there was a relationship between semantic coherence and the level of social ambiguity in each scene. Two participants opted not to complete the New Neighbour and Landlord scene, respectively, and one additional participant’s data was lost due to technological error; these individuals were not included in the analysis.

A 2 (group: cannabis-induced vs. primary psychosis) x 2 (mask: 0ms vs. 160ms) x 2 (condition: steady vs. pulse pedestal) mixed repeated-measures ANOVA was used to assess group differences on the backward masking task and explore whether participants in each group differentially responded to the presence of a mask in either the steady and pulsed pedestal conditions.
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The remainder of the analyses consisted of one-way ANOVAs to compare group scores on pro- and anti-saccadic eye movement, cognitive performance, clinical symptoms, insight into illness, premorbid intellectual functioning, and self-report measures (alcohol use, cannabis use, use of other substances, social anxiety, and trauma).

Finally, a discriminant functions analysis (DFA) was conducted based on the results of the above testing. Variables that could significantly differentiate the two groups, or that showed a trend towards being able to do so, were entered simultaneously into the DFA. Given the novel approach of this research and the lack of strong evidence to justify which variables will contribute most to the discrimination of the groups, a stepwise method was not utilized. Two participants were missing data regarding semantic coherence, and thus were not included in the DFA.
Chapter 3

Results

Participants

The cannabis-induced group was composed of a sample of 16 participants, and the primary psychosis group contained 12 participants. Please refer to Table 1 for descriptive characteristics of the overall sample and by group. The groups did not differ significantly on age, sex, ethnicity, education, marital status, hospitalization history, or tobacco use.

Primary Outcomes

Pro- and Anti-Saccadic Eye Movements

The cannabis-induced group achieved a significantly higher percent correct ($M = 97.78$, $SE = 1.18$) on the pro-saccade task compared to the primary group ($M = 95.00$, $SE = .37$), $F(1, 26) = 6.37, p = .018, \eta^2_p = .20$. Further, the average reaction time on correct trials for the cannabis induced group was significantly faster ($M = .36$, $SE = .028$) on the pro-saccade task than the primary group ($M = .51$, $SE = .051$), $F(1, 26) = 7.32, p = .012, \eta^2_p = .22$. There was no significant difference on performance accuracy on the anti-saccade task between the cannabis-induced ($M = 70.97$, $SE = 3.23$) and primary group ($M = 66.85$, $SE = 6.18$), $F(1, 26) = .401, p = .53, \eta^2_p = .02$, although the cannabis-induced group had a significantly faster reaction time for correct anti-saccade responses ($M = .51$, $SE = .036$) compared to the primary group ($M = .69$, $SE = .084$), $F(1, 26) = 4.85, p = .037, \eta^2_p = .16$.

Interpersonal Competence

On the New Neighbour scene of the SSPA, the cannabis-induced group ($M = 79.33$, $SE = 3.95$) did not differ significantly from the primary psychosis ($M = 83.06$, $SE = 4.33$) group on
Table 1. Descriptive Characteristics of the Overall Sample and by Group

<table>
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<th>Cannabis-Induced (n = 16)</th>
<th>Primary (n = 12)</th>
<th>Total Sample (N = 28)</th>
<th>Statistic</th>
<th>p</th>
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<td>Age M (SD)</td>
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<td>25.17 (5.97)</td>
<td>23.68 (5.12)</td>
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<td>7 (25.0)</td>
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<td>Ethnicity n (%)</td>
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<td>$\chi^2(3) = 3.97$</td>
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<td>1 (3.57)</td>
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<td>Multiple ethnicities</td>
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<td>1 (3.57)</td>
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<td>Highest Education Achieved n (%)</td>
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<td>$\chi^2(4) = 2.14$</td>
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<tr>
<td>Marital Status n (%)</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2(1) = 1.34$</td>
<td>.24</td>
</tr>
<tr>
<td>Never married</td>
<td>16 (100.0)</td>
<td>11 (91.67)</td>
<td>27 (96.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/common-law</td>
<td>0</td>
<td>1 (8.33)</td>
<td>1 (3.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization History n (%)</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2(1) = .097$</td>
<td>.76</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (87.50)</td>
<td>10 (83.30)</td>
<td>24 (85.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (12.50)</td>
<td>2 (16.70)</td>
<td>4 (14.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization Details M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first hospitalization</td>
<td>19.50 (4.36)</td>
<td>22.70 (6.18)</td>
<td>20.83 (5.32)</td>
<td>$t(22) = 1.49$</td>
<td>.15</td>
</tr>
<tr>
<td>Duration of first hospitalization (months)</td>
<td>.42 (3.53)</td>
<td>1.57 (2.66)</td>
<td>.90 (1.79)</td>
<td>$t(22) = 1.60$</td>
<td>.12</td>
</tr>
<tr>
<td>Total number of hospitalizations</td>
<td>1.86 (1.35)</td>
<td>1.80 (1.32)</td>
<td>1.83 (1.31)</td>
<td>$t(22) = -.10$</td>
<td>.92</td>
</tr>
<tr>
<td>Longest hospitalization (months)</td>
<td>.63 (.63)</td>
<td>2.29 (3.08)</td>
<td>1.32 (2.15)</td>
<td>$t(22) = 1.97$</td>
<td>.062</td>
</tr>
<tr>
<td>Tobacco Use n (%)</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2(2) = 1.12$</td>
<td>.57</td>
</tr>
<tr>
<td>Never smoked</td>
<td>3 (18.75)</td>
<td>4 (33.33)</td>
<td>7 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously smoked</td>
<td>3 (18.75)</td>
<td>1 (8.33)</td>
<td>4 (14.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoke</td>
<td>10 (62.5)</td>
<td>7 (58.33)</td>
<td>17 (60.67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SSPA Accuracy, \(F(1,25) = .40, p = .53, \eta_p^2 = .016\). There was also no significant difference between the *cannabis-induced* \((M = 84.46, SE = 2.64)\) and *primary* psychosis \((M = 82.92, SE = 2.74)\) on SSPA Accuracy of the Landlord scene, \(F(1, 24) = .17, p = .69, \eta_p^2 = .007\).

**Speech**

Regarding semantic coherence, a mixed repeated-measures ANOVA revealed a significant main effect of SSPA scene type, \(F(1, 23) = 36.73, p < .001, \eta_p^2 = .77\). There was no significant main effect of group, \(F(1, 23) = 2.623, p = .12, \eta_p^2 = .102\), nor significant interaction between the groups across all three scenes of the SSPA, \(F(2, 22) = 1.41, p = .27, \eta_p^2 = .27\). One-way ANOVAs were conducted to compare semantic coherence between groups across each scene individually. There was no difference between groups on semantic coherence in the Friend scene, \(F(1, 25) = .70, p = .41, \eta_p^2 = .027\), nor the Landlord scene, \(F(1, 24) = .81, p = .38, \eta_p^2 = .033\). However, for the New Neighbour scene, the semantic coherence of the *cannabis-induced* group \((M = .68, SE = .01)\) was significantly higher (more coherent) than the *primary* group \((M = .63, SE = .01)\), \(F(1, 24) = 7.15, p = .013, \eta_p^2 = .23\).

The *cannabis-induced* \((M = 8.93, SE = .45)\) and *primary* \((M = 8.37, SE = .24)\) groups did not significantly differ on the measure of syntactic complexity across all SSPA scenes, \(F(1, 25) = 1.06, p = .31, \eta_p^2 = .04\).

**Backward Masking**

Results from a mixed-model 2 x 2 x 2 ANOVA found a significant main effect of condition, \(F(1,26) = 24.08, p < .001, \eta_p^2 = .48\), and of mask latency, \(F(1,26) = 9.45, p = .005, \eta_p^2 = .267\). There was no significant main effect of group, \(F(1,26) = .23, p = .64, \eta_p^2 = .009\). There were no significant interactions between group and condition, \(F(1,26) = .40, p = .54, \eta_p^2 = .02\), nor group
and mask latency, \(F(1,26) = 1.45, p = .24, \eta^2_p = .053\). There was also no significant interaction between group type, condition, and mask latency, \(F(1,26) = 2.19, p = .15, \eta^2_p = .078\).

![Figure 1](image.png)

*Figure 1.* Mean (SE) semantic coherence by group across each scene of the SSPA. There was a significant difference in coherence ratings in the New Neighbour scene, \(p = .013\).

**Cognition**

On the BACS Digit Symbol Coding test of working memory and processing speed, participants in the *cannabis-induced* group (\(M = 41.56, SE = 4.04\)) were trending towards a better performance than participants in the *primary* psychosis group (\(M = 32.58, SE = 2.66\)), \(F(1,26) = 2.968, p = .097, \eta^2_p = .10\). On the alpha span task measuring working memory, the *cannabis-induced* group (\(M = 38.49, SE = 2.19\) did not significantly differ from the *primary* psychosis group (\(M = 36.10, SE = 1.98\) on their total alpha score achieved, \(F(1, 26) = .610, p = .44, \eta^2_p = .023\).
Figure 2. Mean (SE) percent of trials correct for each group across each pedestal condition and mask duration of the backward visual masking task.
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Secondary Outcomes

Premorbid Adjustment

There was a trend for a difference between the cannabis-induced group ($M = .27, SE = .033$) and primary psychosis group ($M = .39, SE = .055$) on a the PAS, with the cannabis-induced group demonstrating better adjustment to school and relationships before their illness onset compared to the primary psychosis group, $F(1, 26) = 4.03, p = .055, \eta^2_p = .13$.

Illness Insight

There was a trend-level significant difference in illness insight between the two groups, with the cannabis-induced group ($M = 10.63, SE = 1.39$) showing higher levels of cognitive insight into their illness compared to the primary psychosis group ($M = 6.67, SE = 1.44$), $F(1, 26) = 3.77, p = .063, \eta^2_p = .13$.

Clinical Symptoms

There were no significant differences between the two groups on any of the measured clinical symptom domains, as outlined in Table 2.

Table 2

*Means and One-Way ANOVAs for Clinical Symptoms*

<table>
<thead>
<tr>
<th></th>
<th>Induced</th>
<th>Primary / Comorbid</th>
<th>$F(1, 26)$</th>
<th>$p$</th>
<th>$\eta^2_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Symptoms</td>
<td>1.53 (.24)</td>
<td>2.23 (.39)</td>
<td>2.55</td>
<td>.12</td>
<td>.089</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>1.83 (.23)</td>
<td>1.72 (.24)</td>
<td>.11</td>
<td>.74</td>
<td>.004</td>
</tr>
<tr>
<td>Affect</td>
<td>3.09 (.32)</td>
<td>3.25 (.49)</td>
<td>.078</td>
<td>.78</td>
<td>.003</td>
</tr>
<tr>
<td>Resistance</td>
<td>1.90 (.21)</td>
<td>2.11 (.27)</td>
<td>.41</td>
<td>.53</td>
<td>.015</td>
</tr>
<tr>
<td>Activation</td>
<td>1.44 (.15)</td>
<td>1.36 (.16)</td>
<td>.13</td>
<td>.73</td>
<td>.005</td>
</tr>
</tbody>
</table>
Supplemental Outcomes

Social Anxiety

There was no significant difference the cannabis-induced group ($M = 65.50$, $SE = 7.65$) and participants in the primary group ($M = 66.17$, $SE = 9.31$) on their experiences of social anxiety, $F(1, 26) = .003$, $p = .96$, $\eta^2_p < .001$.

Trauma

There was also no significant difference between the cannabis-induced group ($M = 3.88$, $SE = .69$) and the primary group ($M = 3.42$, $SE = .79$) in their number of traumatic events experienced across their lifespan, $F(1, 26) = .19$, $p = .67$, $\eta^2_p = .007$.

Premorbid Intellectual Functioning

The cannabis-induced ($M = 49.56$, $SE = 2.13$) and primary ($M = 47.50$, $SE = 2.20$) groups did not significantly differ on their premorbid intellectual functioning as measured by the WRAT-3 Reading subtest, $F(1,26) = .44$, $p = .51$, $\eta^2_p = .017$.

Cannabis Use

Participants in the cannabis-induced group reported significantly more frequent and hazardous cannabis use ($M = 11.13$, $SE = 2.58$) compared to participants in the primary group ($M = 2.83$, $SE = 1.87$), $F(1, 26) = 5.95$, $p = .022$, $\eta^2_p = .19$.

Alcohol Use

Although participants in the cannabis-induced group reported higher levels of potentially hazardous alcohol use ($M = 7.56$, $SE = 1.63$) than participants in the primary group ($M = 4.08$, $SE = 1.45$), the difference in alcohol consumption between the groups was not significant, $F(1, 26) = 2.36$, $p = .14$, $\eta^2_p = .083$. 
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Substance Use

There were no significant differences between the cannabis-induced ($M = .75, SE = .31$) and primary group ($M = .33, SE = .33$) on other drug use, $F(1, 26) = .82, p = .37, \eta_p^2 = .031$.

**Discriminant Function Analysis**

A discriminant analysis was conducted to determine how well pro- and anti-saccadic reaction time, prosaccade accuracy, semantic coherence (New Neighbour scene of the SSPA), premorbid adjustment, and illness insight (BCIS) classify participants into cannabis-induced or primary psychosis groups. Significant mean differences were observed between groups for all of the predictors on the DV except illness insight ($p = .066$). Although the log determinants were similar, Box’s M indicated that the assumption of equality of covariance matrices was violated ($M = .007$). The discriminant function revealed a significant association between groups and all predictors, $\Lambda = .47, \chi^2(6) = 15.98, p = .014$, accounting for 53.29% of the variation in diagnosis. Closer analysis of the structure matrix revealed all six variables as significant predictors: prosaccade reaction time (-.78), prosaccade accuracy (.53), semantic coherence (.40), anti-saccade reaction time (.72), premorbid adjustment (-.45), and illness insight (.48). The classification showed that 88.5% of the original grouped cases were correctly classified.

Table 3

**Classification Results from Discriminant Function Analysis**

<table>
<thead>
<tr>
<th>Actual Group Membership</th>
<th>Cannabis-Induced</th>
<th>Primary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis-Induced</td>
<td>13 (86.7%)</td>
<td>2 (13.3%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Primary</td>
<td>1 (9.1%)</td>
<td>10 (90.9%)</td>
<td>11 (100%)</td>
</tr>
</tbody>
</table>

*Note. 88.5% of original grouped cases correctly classified. Predictor variables are prosaccade reaction time, prosaccade accuracy, semantic coherence, anti-saccade reaction time, premorbid adjustment, and illness insight.*
Chapter 4
Discussion

The present study was the first of its kind in assessing a neuropsychological approach to the differentiation of cannabis-induced and primary psychosis. A combination of cognitive, visual-processing, and linguistic biomarkers that are characteristic of schizophrenia-spectrum disorders were assessed as potential differentiating variables between induced and primary psychoses. Many of these features, such as impairments in visual perception, disturbances in speech production, and cognitive dysfunction, have been identified since some of the earliest explorations of schizophrenia (Chapman, 1964). They were examined alongside additional measures of psychopathology, illness insight, premorbid functioning, trauma history, and substance use to develop the first attempt as discovering distinguishing endophenotypes between these groups. This study investigated whether these historically-identified, well-replicated features of schizophrenia could be used to accurately differentiate individuals with first-episode psychosis who may go on to develop a schizophrenia-spectrum disorder from those with an induced psychosis that is not indicative of an underlying primary psychotic disorder.

Characterizing Symptoms and Performance of Individuals with Cannabis-Induced Relative to Primary Psychosis

In line with the hypotheses, individuals with cannabis-induced psychosis exhibited significantly better and faster performance on the pro-saccade reaction-time task, showed significantly more coherence of speech in challenging social situations, reported significantly more frequent and hazardous cannabis use, and showed trends towards significantly better premorbid adjustment, less impaired processing speed, and higher levels of illness insight. Contrary to the hypotheses, there were no significant differences between the groups on anti-
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saccade task performance, the visual masking task, syntactic complexity, interpersonal competence, working memory, psychotic and affective symptoms, trauma, or premorbid intellectual functioning.

**Primary Findings**

Previous research has identified impairment in anti-saccadic eye movement in individuals with first-episode psychosis compared to healthy controls (Ettinger et al., 2004). In the present study, although individuals in the cannabis-induced group showed better performance accuracy on the anti-saccade task compared to the primary group, this difference was not significant. It may be that there is impairment across both first-episode groups in anti-saccadic eye movements, though a healthy comparison group would be necessary to confirm this assertion. However, group differences were present on the pro-saccade task. On this task, the cannabis-induced group made very few mistakes, averaging 98% accuracy. The primary group, despite performing well at 95% accuracy, was significantly lower. Though seemingly small, this difference may be clinically meaningful given the ease of the pro-saccade task. It may be that although both groups show impairment on the more challenging anti-saccade task, only the primary group shows impairment on very easy tasks, potentially due to more global or severe deficits in visual and information processing, which are characteristic of schizophrenia (Lencz et al., 2006).

Furthermore, the cannabis-induced group demonstrated significantly faster reaction time to correct responses on both saccade tasks, showing quicker visual processing speed than the primary group.

The groups demonstrated similar interpersonal ability, as measured with the SSPA. First-episode psychosis in general is associated with social withdrawal and impaired social cognition (Lee, Hong, Shin, & Kwon, 2015), making it unsurprising that both first-episode groups
performed similarly. However, although overall social abilities may not be overtly different between groups, more nuanced differences emerged upon closer examination of semantic coherence. Previous research on the SSPA has demonstrated that semantic coherence varies in accordance with the level of ambiguity in a particularly social scene (Woolridge et al., 2019). For example, in the Landlord scene, the social ambiguity is low: participants must negotiate the fixing of a leak in their apartment. However, in the New Neighbour scene, the goal is much more ambiguous: participants are instructed simply to meet their new neighbour, and the onus is on them to initiate and maintain conversation throughout the scene. Both healthy control participants and individuals with schizophrenia show a reduction in semantic coherence from the Landlord to the New Neighbour scene, though individuals with schizophrenia perform significantly worse than healthy controls across all three scenes (Woolridge et al., 2019). In the present study, semantic coherence was not significantly different between the groups across the Landlord or Friend scenes, both of which have relatively clear goals. However, on the New Neighbour scene, the primary group showed significantly less coherence that the cannabis-induced group. It may be that once the goals of a social interaction are less clear, those with a primary psychotic disorder have more difficulty meeting the demands of that interaction, as reflected in their speech coherence. However, this result must be interpreted with caution, given the lack of a significant interaction for semantic coherence across all three scenes.

There was no significant difference between groups on the backward visual masking task. Both the cannabis-induced and primary psychosis groups performed worse on the pulsed-pedestal and delayed-offset mask portions of the task, which is in line with previous findings in healthy control participants. Since the present pilot study does not include a reference group, future research is needed to determine if impairments exist among first-episode psychosis groups.
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compared to healthy individuals as well as how performance compares to individuals with schizophrenia. One explanation for the lack of a significant difference between groups is that impairments in visual backward masking have been found in different at-risk groups, including unaffected siblings of people with schizophrenia, people considered to be prone to psychosis, and individuals with remitted psychosis (Green, Lee, Wynn, & Mathis, 2011). It may be that individuals with cannabis-induced psychosis, despite their lack of an underlying primary psychotic disorder, fall into these at-risk groups and thus are not able to be reliably distinguished by visual masking techniques. However, further research exploring other measures of masking with reference groups would be necessary to reach that conclusion.

Although the cannabis-induced group demonstrated faster average processing speed, this difference was only trending towards significance. It is, however, in line with the above findings demonstrating quicker reaction time on the pro- and anti-saccade tasks. Despite research identifying slower processing associated with cannabis use in healthy populations (Lisdahl, Wright, Medina-Kirchner, Maple, & Shollenbarger, 2014), studies have found that patients with psychosis and a history of cannabis-use disorder have significant better processing speed than patients who do not have a history of cannabis-use disorder (DeRosse et al., 2010). It was hypothesized that there may be a higher functioning subgroup of patients with schizophrenia and comorbid cannabis use (DeRosse et al., 2010), but these findings may also point to the inclusion of individuals with a cannabis-induced psychotic disorder among the cannabis-using group, who, as a whole, may lack a primary or underlying psychosis and therefore experience fewer deficits. Performance on a working memory task was not significantly different between the groups in the present study.
Secondary Findings

The *cannabis-induced* group showed trend-level overall better premorbid adjustment to school and relationships before illness onset compared to the *primary* group. This finding aligns with the neurodevelopmental perspective of schizophrenia, which emphasizes the lifelong cognitive, social, and functioning difficulties associated with the illness (Owen, O’Donovan, Thapar, & Craddock, 2011). It suggests that *cannabis-induced* psychosis may not be associated with the same extent of developmental impairment as *primary* psychosis, but rather that the apparent difficulties may occur in a more acute state of illness. As a result, functional recovery may be more attainable in this group following symptom remission.

Similarly, the *cannabis-induced* group showed, at a trend-level, better insight into their illness than the *primary* group. Since schizophrenia is characterized by a lack of insight into one’s illness (Beck et al., 2004), this finding represents a notable difference between the two diagnoses. Given that a lack of insight is tied to the maintenance of delusional thinking and treatment resistance (Beck et al., 2004), this finding may point also to the potential for recovery following a substance-induced psychosis.

No significant differences emerged between the groups across other psychiatric symptoms, including positive and negative symptoms, affect, resistance, and activation. Average symptom scores were relatively low across both groups, typically falling within the mild range. Previous research identifying differences in symptoms has been inconsistent (Wilson et al., 2018). This inconsistency may be a result of the timing of assessment, with symptom differences possibly being clearer as individuals enter first-episode programs and before they have begun treatment to reduce symptoms. However, despite being contrary to the initial hypothesis of the present study, the lack of significant symptom differences is not altogether unsurprising – the similarities
between symptoms in both groups is one of the core contributing factors to the difficulty differentiating the two diagnoses. Given the high heterogeneity of symptom presentation across individuals with first-episode psychosis, it may be unlikely that any particular constellation or severity of clinical symptoms is more diagnostically relevant than another.

Interestingly, despite previous research showing that likelihood of trauma is approximately 23 times greater among individuals with substance-induced compared to primary psychosis (Fraser et al., 2012), this effect did not emerge in the present study. The Brief Trauma Questionnaire used in the present study, however, was limited to 13 items, each assessing a unique type of traumatic experience. This type of scale notably does not assess the frequency of any one traumatic experience (e.g., someone who has experienced three car accidents would have the same score as someone who has experienced one car accident), and thus may not allow for enough sensitivity to differentiate between groups. However, it is also important to consider that individuals with psychosis are at an increased risk of physical and sexual victimization and assault; one study found up to 67% of psychosis patients had been victimized in adulthood (Bengtsson-Tops & Ehliasson, 2011; Dean et al., 2007; Fitzgerald et al., 2004. Common risk factors may place both groups at an increased chance of traumatic experiences.

As expected, the cannabis-induced group reported significantly more frequent and hazardous cannabis use compared to participants in the primary group. Based on the scoring cut-offs identified by the scale creators (Adamson et al., 2010), the cannabis-induced group, on average, fell within the DSM-5 identification of mild cannabis use disorder, whereas the primary group, on average, did not even meet the lowest criteria of hazardous cannabis use. For alcohol use, the cannabis-induced group were scored, on average, four points higher on the scale (which was out
of 40) compared to the primary-comorbid group, but this difference was not significant. The average of both groups fell below the cut-off for hazardous alcohol use (Babor et al., 2001).

Utility of the Present Findings for Predicting Diagnostic Classification

The potential of certain symptoms to successfully predict group membership in the present sample was explored in this investigation. The goal of this exploration was to determine if the assessment of certain differentiating symptoms would help to improve the certainty of clinician diagnoses, rather than for making definitive diagnoses. Symptoms that showed a significant or trending difference between groups were included in the analysis: pro-saccade reaction time, pro-saccade accuracy, semantic coherence, anti-saccade reaction time, premorbid adjustment, and illness insight. Overall, this analysis was significant, and correctly classified 88.5% of the current sample. Interestingly, only two of these predictors (premorbid adjustment and illness insight) have been previously explored in the literature. The remaining symptoms (pro-saccade and anti-saccade reaction time, pro-saccade accuracy, and semantic coherence) were all novel to the present study, and are all representative of core neuropsychological deficits in schizophrenia. This finding provides support for the notion that characteristic symptoms or endophenotypes of schizophrenia may have utility in being able to differentiate cannabis-induced from primary psychoses in a first-episode sample.

Our results are in line with the few studies that have explored the predictive power of certain symptoms in differentiating between diagnoses in first-episode psychosis. In an early investigation, Rosenthal and Miner (1997) found significant differences between substance-induced psychosis and schizophrenia in areas including bizarre delusions and formal thought disorder, history of methadone maintenance, detoxification, and cocaine abuse, and suicidal ideation; together, these variables correctly classified 70.4% of patients. Rubio and colleagues
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(2012) successfully classified 96% of cases between *cannabis-induced* psychosis and primary psychotic disorders, with predictors including depression and interpersonal sensitivity. Fraser and colleagues (2012) utilized variables including current cannabis dependence, trauma history, and the absence of a family history of psychosis, and was able to correctly identify 78.7% of patients with a substance-induced (not specific to cannabis) psychotic disorder from those with a primary psychotic disorder. Although the aforementioned studies have had some success in classifying these disorders, the types of predictors used are not consistent across studies, pointing to the need for further research to explore and replicate these differences in future samples. Furthermore, many of these studies utilize cannabis or other drug use as prominent predictors in their models. This predictor was omitted from the current analysis, given that heavy cannabis use is very closely intertwined with the independent variable and its inclusion creates the risk of the model being tautological in nature.

It is important to also emphasize that the discriminant function analysis in the present study was conducted post hoc based on our evaluation of which functions in the sample best discriminate between the groups. As such, it is necessary to collect new data to cross-validate the utility of the analysis. If a future study is able to confirm the current classification by successfully classifying new cases, this would provide more evidence for the predictive validity of the model, and could eventually provide clinicians with a useful tool to improve the certainty of diagnoses in first-episode psychosis.

**Limitations and Future Directions**

This current study has pioneered some of the first data exploring the use of core neuropsychological features of schizophrenia as a means to differentiate between individuals with *cannabis-induced* and *primary* psychoses. A combination of variables assessed in just one
two-hour session allowed the differential classification of individuals with the two diagnoses with 88.5% accuracy. The study also produced findings that help to clarify a sparse, inconsistent literature base, and has brought new ideas to advance future research. However, these findings should be considered alongside limitations.

This research addresses an area where diagnostic clarity is uncertain given the similarities in symptom presentation across cannabis-induced and primary first-episode psychosis. As a direct result of the uncertainty that is the motivating factor for this study, it is possible that individuals in either the cannabis-induced or primary groups may have been incorrectly placed into those groups as a result of a misdiagnosis. Despite the best efforts of attentive and highly competent clinicians, diagnoses in first-episode psychosis can be somewhat unstable (Fusar-Poli et al., 2016). Although meta-analytic research has found the prospective diagnostic stability of schizophrenia to be quite stable (0.90), substance-induced psychosis shows significantly lower stability (0.66; Fusar-Poli et al., 2016). Future research that assesses and classifies individuals upon their entry to a first-episode program would benefit from including follow-up periods to confirm the accuracy of their predictions over time.

Furthermore, many individuals in the primary group also either currently use cannabis or have in the past. Given that cannabis use has been associated with negative outcomes in first episode psychosis in general (Barrowclough, Gregg, Lobban, Bucci, & Emsley, 2014; Seddon et al., 2016; Oluwoye et al., 2017; Schoeler et al., 2016), it is difficult to determine which symptoms may be more closely related to varying levels of cannabis use, or which may be related to unique diagnoses. In addition, given that the cessation of cannabis and other substance use is encouraged very early in treatment, individuals in the cannabis-induced group may have already ceased using cannabis by the time of their participation in the present study. All
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individuals were also being treated with medication at the time of participation. It is also difficult to isolate the use of any one specific substance due to the fact that many individuals report using multiple substances, and many research studies discuss “substance-induced psychosis” as a whole without a narrowed emphasis on a particular substance. Future research should assess individuals in more acute stages of illness, prior to intervention, to assess whether symptom differentiation at this time point is consistent with the present study. Future research should also attempt to isolate the effects of specific substances.

In order to enhance the mobility of the study to be able to reach a wider group of participants, eye movements were assessed using a reaction time-based computerized task rather than with an eye-tracker. The use of accessible and cost-effective tools allows for this research to be applied by clinicians in clinical settings. However, this method of measurement suffers from certain limitations. For example, relying on participant keypresses introduces additional confounds, such as motor or memory impairments. This method also does not allow for the direct measurement of saccadic eye movement, but rather uses a participant’s ability to respond correctly to a task as a proxy. Future studies should utilize eye-tracking to assess pro- and anti-saccadic eye movements in order to further validate this effect. Furthermore, the pro-saccade task demonstrated low internal consistency, which represents a limitation of this part of the task. However, due to the ease of the task and the resulting very low frequency of errors, it may be that split-half method is not the most appropriate measure of the internal consistency for this task.

Despite its overall breadth, the present study was limited in the cognitive domains that it assessed. Due to constraints on the length of the study, only tests of working memory and processing speed were used. Research has identified a much larger array of areas of cognitive deficits in schizophrenia (e.g., verbal learning, attention, memory; Bowie & Harvey, 2005) that
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should be addressed in future research. Individual subtests may be affected by a variety of external factors, such as motor impairments or attentional difficulties, that could affect perceived performance in a certain domain. A more extensive battery of tests would allow for the comparison of both cognitive composite scores as well as more discrete abilities between the groups.

Finally, this proof-of-principle pilot study represents only the beginning of work in what is positioned to become a much larger body of literature. Our research should be noted for its novel approach to assessing differential clinical presentations and symptomatology in first-episode psychosis. Several aspects of the study were novel, serving to both replicate and build upon previous research. At present, this study is limited by a small sample size that may affect the interpretation of the results. However, statistical significance and strong effect sizes allow us to draw some supported conclusions regarding the interpretation and implications of the study. Furthermore, it is important to note that the present study is cross-sectional in nature, capturing only a snapshot of an individual’s clinical presentation and specific impairments. Given the potential for symptoms in early psychosis to change, future studies should aim to include follow-up assessments to explore whether the classifications made remain stable over time. Prospective research might assess individuals upon their entry to a first-episode psychosis program and monitor their diagnostic process over time to determine the predictive power of neuropsychological diagnostic tools.

As future studies continue to explore this relatively new area of research, it will be beneficial to place more emphasis on assessment integrity, depth, and sensitivity within each domain. The present study served as an initial exploration of this topic, with an emphasis on breadth to
DIFFERENTIATING CANNABIS-INDUCED AND PRIMARY PSYCHOSIS

account for the sparse literature in this area. It has provided evidence for early signals that future research can target with more extensive batteries of tests.

Implications and Conclusions

The current study revealed several findings that may be instrumental in furthering the understanding of differences and core characteristics of cannabis-induced and primary psychosis. These findings can be used to spur future research efforts to identify factors that will aid in the clarification of diagnosis in a first-episode context. These findings are also useful in their contribution to a small and variable literature base. Given the heterogeneity of symptoms and the inconsistency of previous literature thus far, more studies are needed to contribute to and clarify existing findings.

This study was motivated by an emerging diagnostic crisis that clinicians are facing in terms of knowing when certain diagnoses should be given, whether to initiate antipsychotic treatment, or whether patients should be treated at a cannabis clinic or a psychosis clinic. Reliance on a clinical interview or traditional diagnostic tools is insufficient to make this diagnostic distinction and often leads to a lengthy process of diagnosis. This study introduces measures that are sensitive to schizophrenia and less likely to be found in cannabis-induced disorders as a means to differentiate these disorders and work towards a model that would help clinicians make reliable distinctions between them. Methods of differential diagnosis would facilitate more rapid and streamlined early-psychosis program entry, improve individualized treatment plans, and reduce the diagnostic load on the mental health care workers, leading to widespread beneficial short-term and long-term outcomes in these groups.

Improved measures of differentiation may also lead to reductions in misdiagnoses or improper diagnostic classifications. Studies often highlight the rates of conversion from a
DIFFERENTIATING CANNABIS-INDUCED AND PRIMARY PSYCHOSIS

substance-induced to a primary psychotic disorder, exploring the “conversion” or “transition” to schizophrenia. This conceptualization may be misleading; rather than a “conversion”, which implies the progression of a singular illness, the change in diagnosis may be due to an original misdiagnosis. For example, many studies that look at rates of “conversion” may be affected by poor measures of diagnostic classification that incorrectly classify psychosis with comorbid cannabis use as cannabis-induced psychosis. In other cases, what was identified as cannabis-induced psychosis may have been, in reality, the onset of schizophrenia. As such, it is possible that the similarities between the two illnesses, in combination with the high rates of cannabis comorbidity, lead to misdiagnoses that may lie uncorrected for years. This is especially concerning given that determining the primacy of a disorder is closely related to the decision to initiate antipsychotic treatment. Misdiagnoses can result in either unnecessary, prolonged use of antipsychotic medication, or hesitation in prescribing medication that leads to a lengthier duration of untreated psychosis. Furthermore, it may lead to the experience of stigmatization or self-stigma associated with receiving a diagnosis.

Overall, the use of substances remains a significant diagnostic challenge in first-episode psychosis clinics. Obtaining an accurate diagnosis is crucial to early intervention and treatment in first-episode psychosis, as it allows for individualized and appropriate treatment planning. Our study represents a promising start towards investigating the neuropsychology of cannabis-induced and primary psychoses, and supports the use of neuropsychological methodology to aid in the clinical differentiation of these disorders. Ultimately, our research serves to both highlight the vast potential in this area, as well as demonstrate the critical need for further investigation to improve outcomes for individuals with psychosis.
DIFFERENTIATING CANNABIS-INDUCED AND PRIMARY PSYCHOSIS

References


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Appendix A:
Queen’s University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) Approval of Study

QUEEN’S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

October 26, 2018

Ms. Woolridge
Department of Psychology
Queen’s University

ROMEO/TRAQ #: 6024769
Department Code: PSYC-219-18
Study Title: "Substance Use, Language, and Cognition in Psychosis"
Supervisor: Dr. Christopher R Bowie
Review Type: Delegated
Date Ethics Clearance Issued: October 26, 2018
Ethics Clearance Expiry Date: October 26, 2019

Dear Ms. Woolridge,

The Queen’s University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Letter of Information/Consent Form v3 2018OCT25
- Liebowitz Social Anxiety Scale v2 2018OCT14
- BACS Scoresheet v2 - De-Identified version 2018OCT14
- Alcohol Use Disorders Identification Test (AUDIT) uploaded date 2018SEP19
- Beck Cognitive Insight Scale (uploaded date 2018SEP19)
- Brief Trauma Questionnaire (uploaded date 2018SEP19)
- Cannabis Use Disorders Identification Test (uploaded date 2018SEP19)
- NIDA Substance Use Checklist (uploaded date 2018SEP19)
- Modified Premorbid Adjustment Scale (MPAS) uploaded date 2018SEP19
- WRAT 3 Reading Scoresheet (uploaded date 2018SEP19)
- WRAT 3 Reading Instructions (uploaded date 2018SEP19)
- BACS Instructions (uploaded date 2018SEP19)
- Letter Number Sequencing Scoresheet (uploaded date 2018SEP19)
- Letter Number Sequencing Instructions (uploaded date 2018SEP19)
- Social Skills Performance Assessment (SSPA) Training Manual version 3.2
- Brief Psychiatric Rating Scale (BPRS) Expanded Version (4.0)

Documents Acknowledged:
- CORE training certificate S. Woolridge 2015MAY12
- Heads Up! program approval v.2018OCT11
**Amendments:** No deviations from, or changes to the protocol should be initiated without prior written clearance of an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involve(s) only administrative or logistical aspects of the trial.

**Renewals:** Prior to the expiration of your ethics clearance you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented on the renewal form.

**Completion/Termination:** The HSREB must be notified of the completion or termination of this study through the completion of a renewal report in ROMEO.

**Reporting of Serious Adverse Events:** Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after study team members have become aware of the information.

**Reporting of Complaints:** Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of study team members becoming aware of the complaint.

**Note:** All documents supplied to participants must include the contact information for the Research Ethics Board. Investigators: please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Yours sincerely,

Albert F. Clark, PhD

Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision
### Appendix B: Reliability

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*Note.  

$^a$ Internal reliability was calculated using Cronbach’s alpha.

$^b$ Internal reliability was calculated by adjusting split-half (odd-even) correlations with the Spearman-Brown prophecy formula.

$^c$ Pearson correlation coefficients were calculated between percent correct scores on odd and even trials.

** $p < .01$
## Appendix C:

### Bivariate Correlations Among Study Variables

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<td>BPRS Positive Symptoms</td>
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<td>-.174</td>
<td>.182</td>
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<td>-.124</td>
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<td>-.087</td>
<td><strong>.776</strong></td>
<td>.041</td>
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<td>BPRS Resistance</td>
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<td>-.207</td>
<td>-.355</td>
<td>.046</td>
<td>.172</td>
<td><strong>.704</strong></td>
<td><strong>.434</strong></td>
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<td>BPRS Activation</td>
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<td>.123</td>
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<td>.230</td>
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*Note.* *p < .005, ** p <.001.