The Effects of Nabilone and Dexamphetamine on three underlying Schizotypy Dimensions of Delusions/Hallucinations, Mania and Delusional Guilt

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(ACTRN12618001292268), the Therapeutic Goods Administration (TGA Clinical Trial Repository CT-2018-CTN-02561-1).

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ABSTRACT

Schizotypy encompasses the broader expression of schizophrenia-like traits/states within the general population. As such it may be used as an investigative model of schizophrenia in healthy volunteers without confounding issues of antipsychotic treatment, a major issue in schizophrenia research. Amphetamines and cannabinoid agonists have both been implicated in schizophrenia and suggested to be associated with psychotic illnesses, with strong evidence for the former having a causal role but weak and disputed evidence for the latter. This study aimed to assess the effects of a CB receptor agonist, Nabilone (1-2 mg, PO, bid) on schizotypy in relation to a previous study on the psychomimetic Dexamphetamine (DEX, 0.45 mg/kg, PO, qd) to investigate the potential roles of cannabinoids and dopamine in underlying schizotypy structure, schizotypy components and potential psychomimetic or antipsychotic effects.

Methods: Healthy volunteers (n=24) completed a within subject, double-blind, placebo-controlled crossover experiment with permuted block randomisation for drug order wherein they received Nabilone and completed a range of schizotypy measures, drug effect and mood questionnaires as well as the Phantom Word Illusion as a possible index of susceptibility to auditory hallucinations. A Multiple Factor Analysis (MFA) was used to identify underlying dimensions of schizotypy under DEX and Nabilone with permutation tests to determine drug significance.

Results: Nabilone had no significant effect on overall schizotypy compared to DEX which caused a significant overall increase. The MFA of combined Nabilone and DEX data identified three primary underlying dimensions of schizotypy: Delusions and Hallucinations; Mania-like; Delusional Guilt. Nabilone and DEX had significant effects on different dimensions with Nabilone increasing scores of Delusional Guilt and DEX increasing scores.
of Mania-like symptoms (Energy, Bizarre Behaviour, and Euphoria). Neither significantly affected the primary component of Delusions and Hallucinations. Nabilone also significantly increased Amphetamine-Opposite subscales and the Marijuana Mood Questionnaire, while DEX significantly increased Amphetamine-Like Subscales and anxiety measures. DEX increased the number of phantom words reported in the Phantom Word Illusion, potentially indicative of greater likelihood of auditory hallucination experience, while Nabilone had no significant effect on this measure.

**Conclusion**: Nabilone prompted the significant expression of specific underlying schizotypy symptoms related to delusional guilt, which may indicate a limited but potential role of cannabinoids in the expression of specific schizophrenia-like symptoms. The different effects of Nabilone and DEX on overall schizotypy, underlying schizotypy dimensions and associated mood states combined with the significant effect of Nabilone on amphetamine-opposite like effects may suggest that cannabinoid agonists have a net decreasing effect on dopamine release but may induce some types of psychotic-like symptoms independent of dopamine.
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ABBREVIATIONS

AMQ-L - Amphetamine Mood Questionnaire (Amphetamine Like)
AMQ-O - Amphetamine Mood Questionnaire (Amphetamine Opposite)
ANOVA - Analysis of Variance
ARCI-MQ - Addiction Research Centre Inventory Marijuana Questionnaire
BPRS-E - Brief Psychiatric Rating Scale - Expanded
CB - Cannabinoid Receptor
CB1 - Cannabinoid Receptor Type 1
CB2 - Cannabinoid Receptor Type 2
CNS - Central Nervous System
D1 - Dopamine Type 1 Receptor
D2 - Dopamine Type 2 Receptor
GABA - γ-amino Butyric Acid
GPCR - G-protein Coupled Receptor
ICD-10 - International Statistical Classification of Disease 10th Edition
LSHS-R - Launay Slade Hallucination Scale - Revised
MIS - Magical Ideation Scale
MFA - Multiple Factor Analysis
MTB - Marteau-Bekker Self Evaluation Questionnaire
PECAN - Perceptual Effects of Caffeine and Nabilone Clinical Trial
PET – Positron Emission Tomography
PAS - Perceptual Aberration Scale
PCA - Principal Component Analysis
PWI - Phantom Word Illusion
SAPS - Scale for the Assessment of Positive Symptoms
Δ9-THC - Δ9-Tetrahyrdrocannabinol
1. Introduction and Background

1.1 Schizophrenia

Schizophrenia is a severe and frequently chronic neuropsychiatric disorder characterised by distortions in thinking, perception, behaviour, and affect that is inappropriate or blunted (ICD-11). Despite an estimated lifetime prevalence of only 1% (Tandon et al., 2009), the burden of schizophrenia is substantial. In the United States alone, an annual estimated economic burden of 60 billion dollars is attributed to the disorder (Huey Yi et al., 2016). Individuals diagnosed with schizophrenia are more likely to be homeless, unemployed and reliant upon family, community or medical support systems and for long periods of time, often from late adolescence until old age (Charlson et al., 2018). Schizophrenia is associated with significant reductions in life expectancy with effected individuals living an estimated average 15 years less compared to the general population and displaying increased mortality rates at every age (Laursen et al., 2014; Whiteford et al., 2015; Saha et al., 2007). Links with metabolic syndrome, smoking, poor diet and sedentary lifestyles also contribute to an overall poorer physical health profile (Laursen et al., 2012; Saha et al., 2007). Treatments are limited and have not progressed far beyond early antipsychotic drugs, and of those diagnosed only an estimated 35% reach clinical and social recovery criteria (Jääskeläinen et al., 2012). Despite over a century of research, the exact aetiology of schizophrenia remains unknown. There is a
general consensus that the disorder results from the complex interactions of a number of different risk factors, including genetic polymorphisms, neurodevelopmental abnormalities, prenatal and neonatal insults, and biological, psychosocial and environmental stressors. It is believed that these factors, and their interactions, cumulatively increase the risk for the development of schizophrenia (Howes and Kapur, 2009).

The lack of distinct biological markers makes a diagnosis of schizophrenia almost entirely based upon signs and symptoms (ICD-11). A broad range of symptoms have been linked to schizophrenia, and it is often conceptualised as a heterogeneous group of disorders as opposed to a single pathology. There is practical utility in a categorical diagnostic approach for psychiatric disorders, based primarily on the same or very similar treatment for all psychotic illnesses. However, there are valid arguments for a less dichotomous approach, chiefly related to treatment-resistant individuals and differences in long-term outcomes. For example, relatively cognitively-spared people with schizophrenia tend to have much better outcomes, frequently with full remission, and are more responsive to drug treatment, but also tend to have more florid psychotic symptoms, whereas those with greater cognitive impairment tend to have poor outcomes, treatment resistance, and are more likely to have negative symptoms (Hallmayer et al., 2005). Frequent fluctuations of disorder expression across and within an individual’s life make it difficult to categorise, especially as most diagnostic parameters require numerous episodes and chronic disability (Nelson et al., 2013).

There is also compelling evidence for the presence of these symptoms within the general population or in those who would be considered psychologically healthy (Meehl, 1962; Verdoux and van Os, 2002; Modenato and Draganski, 2015). This has led to the creation of theories that allow for the notion of schizophrenia as a continuum opposed to a wholly categorical phenomena, with a spectrum within the general population of associated traits, or, ‘schizotypy’.
1.2 Schizotypy

1.2.1 Concept and conceptual issues

The idea of schizotypy, a contraction of ‘schizophrenia phenotype’, was first introduced over 60 years ago by Rado and Meehl, to encompass the broader expression of schizophrenic-like psychopathology and impairment. It described schizotypy as a form of latent personality organisation, a collection of inherited traits that qualitatively mirrored those observed in schizophrenia and reflected a putative liability towards the development of the disorder (Meehl, 1962; Rado, 1953; Modenato and Draganski, 2015). Conceptually, there is some dispute in regard to different theoretical models of schizotypy, trait vs state distinctions and its relative use and relevance within research. Studies of schizotypy are usually predicated on one of two competing theories, the quasi-dimensional or fully dimensional model, that differ in fundamental assumptions regarding schizophrenia risk, psychosis-proneness and population distribution (Grant et al., 2018).

1.2.1.1 Quasi-dimensional Model

The Quasi-dimensional, or Meehlian, model holds origins in Rado’s genetically liable schizotypy and was heavily elaborated upon in Meehl’s 1962 disease model theory of mental illness. This model suggests that schizotypy is specific to a group of affected individuals with the remaining population not at risk. The schizotypic group were believed to have an ‘integrative neural defect’ due to a specific ‘schizo-gene’ that was characterised by a dominant pattern of inheritance (Grant et al., 2018). The risk of progression to clinical schizophrenia was determined by the interaction of polygenetic potentiators with genetic factors that influenced this ‘schizogene’. It was not presumed that all cases of schizotypy would transition to a clinical case, rather 10% of the 10% of schizotypes in the general population would subsequently transition clinically to the illness state. Barring
acknowledgement of potential levels of disease expression and development, it was an otherwise categorical perspective where an individual either had a genetic predisposition or did not (Nelson et al., 2013). As a theory it is largely unsupported by taxometric analysis or genetic studies, with the idea of one specific responsible gene at odds with the broadly accepted polygenetic conceptualisation of schizophrenia. Meehl also did not accept that schizotypy was present outside of the identified subcomponent of the population and there is substantial evidence of anomalous perceptual experiences and self-reported psychotic-like experiences within the general population (Meehl, 1962; Verdoux and van Os, 2002; Modenato and Draganski, 2015).

1.2.1.2 Fully Dimensional Model

The fully dimensional model pioneered by Hans Eysenck presented the idea of continuous personality dimensions, from low schizotypy and psychologically healthy to high schizotypy expressed as schizophrenia. Eysenck’s model encompassed genetically rooted dimensions of personality that interacted with the environment and were expressed phenotypically via biological intermediaries (Grant et al., 2018; Eysenck, 1950; Eysenck and Barrett, 1993). This model was then extended by Claridge to suggest that schizotypy resulted from an interaction of polygenetic and environmental determinants normally distributed within the general population as enduring personality traits (Claridge, 1997). Where Eysenck denoted a boundary within the schizotypy continuum that distinguished between health and illness, Claridge proposed that there was a multidimensional set of traits that vary along the continuum of the population and do not necessarily lead to psychopathology; rather, there are a number of other contributing factors. This approach accounts for the anomalous experiences within the general population and aligns with current theories of schizophrenia. Like the quasi-dimensional model, the fully dimensional model notes that it is the presence of schizotypal traits in combination with other aetiological risk actors that confer a risk for
psychopathology (Rawlings et al., 2008; Nelson et al., 2013). High schizotypy does not also necessarily confer dysfunction; indeed, individuals who have scored highly on schizotypic measures have been shown to have subjective wellbeing (Goulding, 2004). Studying schizophrenia using a fully dimensional model of schizotypy allows for a dynamic and developmental bottom up approach. It can be used for the identification of potential contributing factors along the breadth of the schizotypic continuum or insight into proposed mechanisms, integrating the subclinical along with the clinical.

1.2.1.3 Trait vs. State

Aside from debates surrounding conceptual models there is also often confusion regarding the dual trait vs state nature of schizotypy. That is, the trait-like personality as well as the symptom state of an illness, and that schizotypy can encompass both, often without a distinct separation between the two domains. An individual with high trait schizotypy who regularly experiences symptoms is different to a state of high schizotypy that reflects a transient fluctuation from normal behaviour. Or, a state may be derived from a fluctuation of a personality trait. Subclinical schizotypal traits have been found to account for over half of the variance in psychotic expression (Van Os et al., 2009), which supports the idea that expression may vary as a function of traits but that specific states can also contribute.

1.2.2 Schizotypy Components

There is a general acceptance of a multi-dimensional schizotypy structure (Liddle, 1987; Bentall et al., 1989; Vollema and van de Bosch., 1995; Lenzenweger and Dworkin., 1996; Kwapił and Barrantes-Vidal., 2008; Cicero and Kerns., 2010; Kwapił and Barrantes-Vidal., 2014). However, the number and content of those dimensions is in some dispute. The most commonly referenced factor structure includes three primary subgroups of symptoms: positive, negative and disorganised. Positive symptoms are classified as those which add to or
augment normal function (Andreasen et al., 1995). This encompasses symptoms of psychosis and includes delusions, hallucinations, thought disorder, and bizarre or disorganised behaviour (Randrup and Munkvad, 1972; Fusar-Poli et al., 2012). Delusions are fixed, implausible false beliefs that are maintained even when contradicted by compelling evidence and rational arguments. Delusions can occur in many different forms including persecutory delusions, somatic delusions, delusions of reference, delusions of control, delusions of guilt or sin, delusions of jealousy and delusions of mind reading. Of these delusions, persecutory delusions are the most commonly reported delusions in schizophrenia and are present in 80% of individuals (Sartorius et al., 1986; Stompe et al., 1999). Hallucinations are sensory perceptions with no corresponding external stimuli (Andreasen et al., 1995). These perceptions can occur in any of the sensory modalities (auditory, visual, somatic, olfactory, tactile and gustatory) to differing degrees of severity. The most common hallucinations in schizophrenia are auditory hallucinations which are found in approximately 70% of people with the disorder (Mueser et al., 1990). Following auditory hallucinations, the general hierarchy of hallucination prevalence follows visual, tactile and olfactory (Jablensky., 1997; Thomas et al., 2007). Positive symptoms are often considered the most marked symptoms of schizophrenia, with the vast majority of patients clinically presenting initially due to the presence of psychosis. Those patients who present predominantly with psychotic symptoms are more responsive to treatment and have a greater likelihood of remission (APA, 2013). Negative symptoms are reductive and are those which reflect an absence or impairment of normal function and behaviours. These symptoms include blunted affect, emotional withdrawal, alogia, asociality and loss of motivation (Kay et al., 1987; Andreasen, 1982). Compared to positive symptoms, negative symptoms are associated with a poorer quality of life, both in individuals diagnosed with schizophrenia and those classified as high schizotypy (Cohen et al., 2009; Milev et al., 2005). Antipsychotic treatments have been shown to have
only a modest effect on negative symptoms and in schizophrenia correlate with a poorer prognosis, with the severity of symptoms a predictor of chronic disability (Perkins et al., 2005). Schizophrenia has also been linked to general cognitive deficits (Tandon et al., 2009) with impairments in attention, working memory and executive function (Heinrichs and Zakzanis, 1998) in a subpopulation that may be as high as 50% of people with schizophrenia (Hallmayer et al., 2005). Similar cognitive deficits have been observed consistently within schizotypy although the magnitude and scale can vary (Nelson et al., 2013). Cognitive impairments as group averages are observed in individuals with schizophrenia and people at a high risk for schizophrenia (Pukrop and Klosterkötter, 2010) but also vary immensely. Cognitive impairments tend to be more severe in chronic schizophrenia and occur at greater incidence in individuals who have negative symptoms (Hallmayer et al., 2005). Interestingly, the highest risk factor for brain cell loss is dose and duration of antipsychotic drug treatment, with antipsychotic drug treatment negatively correlated with cognitive performance (Ho et al., 2011). Some have argued that the cognitive impairments in schizophrenia may be more strongly linked to motivational and attentional factors than other cognitive processes (Moritz et al., 2017). Therefore, the association of cognition, especially working memory, with schizophrenia is presently unclear.

The positive, negative, and disorganized three-factor model of schizophrenia has been supported in both clinical and non-clinical populations and is the most commonly referenced model in schizotypy factor structure studies. However, there is also evidence for two factor models of positive, and negative symptoms (Siever and Gunderson, 1983; Kendler et al., 1991), different three factor models with replacements of the cognitive or disorganized dimension (Bergman et al., 1996) or with the addition of disordered relationships (Strauss et al., 1974). There has been evidence for a four-factor model that includes: an interpersonal latent factor; cognitive/perceptual latent factor; disorganized latent factor; and latent paranoid
factor (Wuthrich and Bates, 2006; Stefanis et al., 2004), or other three-factor models that adjust correlations, or assignations, of paranoia, magical ideation, delusions of reference and social anxiety to different dimensions (Wuthrich and Bates, 2006). As such, limiting assessment of schizotypy to the traditional three factor model may mean limiting potential further insight into specific neurological mechanisms. Previous broader assessments of schizotypy symptoms outside of existing factor structures have identified different or more specific domains (Grover et al., 2018). It is especially important to consider a variety of symptoms in disorders such as schizophrenia which are heterogenous in nature.

1.3 Neural Substrates

1.3.1 Genetic contribution

Meehls’ first model of schizotypy presented a single dominant risk allele that when combined with the environment formed a genetic basis of risk. As of today, over 8300 independent polymorphisms have been identified as potential contributors towards the risk of development of schizophrenia (Ripke et al., 2013; Barrantes-Vidal et al., 2015). This large number of alleles supports a continuous nature, or dimensional model, of schizotypy.

Schizophrenia estimates of heritability vary. A meta-analysis of twin and family-based studies suggested an estimated 81% heritability component (Schwab and Wildenauer, 2013; Sullivan et al., 2003) while genome wide association studies of single-nucleotide polymorphisms propose a more modest 60-70% estimate (Greenwood et al., 2007). Family relation or family history of schizophrenia remains the biggest risk factor for the development of the disorder with the degree of relation and proportion of shared genes denoting the level of risk. For example, second degree relatives infer a risk of 2-4% compared to 10-15% for first degree relatives. Monozygotic twins have an estimated 45% risk of development, which allows for a role of environmental and other contributing risk factors. However, one of the
main twin studies that is often cited as evidence for a high genetic component (up to 60%) actually provided evidence of a strong uterine environmental role. That is, while identical pairs that shared a placenta had a 60% chance of both being diagnosed with schizophrenia, that fell to under 11% in those that had separate placentae (O Davis et al., 1995). Most twin studies do not take into account the number of placentae per birth, and hence cannot avoid this confounding influence. Identifying specific genes is difficult due to the multi-faceted aspect of schizophrenia and the complex interaction of genetic and non-genetic factors. A few genes that have been implicated include those that code for proteins involved in dopamine and glutamate signaling, neurodevelopment and immune function but by far the majority have not been associated with schizophrenia in any biological fashion. Many of these genes have also been linked to schizotypy, with endophenotypes linked to schizophrenia also associated with high schizotypy in non-clinical samples and the general population (Ettinger et al., 2011). Debatably the most examined allele in schizophrenia is nucleotide polymorphism rs4860 which plays a role in influencing dopaminergic neurotransmission. Polymorphism rs4860 has been associated with schizotypic traits and has been differentially related to the different schizotypy dimensions (Schürhoff et al., 2007). However, as is the rule rather than the exception in genetic studies of schizophrenia, there are also studies that reject this association, with differing evidence of correlations with increased negative schizotypy, perceptual aberration, total score or even a reverse effect (Ma et al., 2007; Ettinger et al., 2006; Okochi et al., 2009).

1.3.2 Environmental factors

A number of environmental factors have been identified as risk factors in the development of schizophrenia, with potential influence from perinatal periods to adulthood. Perinatal and postnatal risk factors include paternal age (Sipos et al., 2004; Torrey et al., 2009), prenatal viral infections such as herpes or influenza (Yolken, 2004), placenta
insufficiency (Mallard et al., 1999; O Davis et al., 1995; Rehn et al., 2004); pregnancy complications such as bleeding (Byrne et al., 2007), abnormal fetal development (Wahlbeck et al., 2001) and delivery complications such as asphyxia (Geddes et al., 1999). Exposure to trauma during childhood or early adolescence be it physical, emotional or sexual, poor family relationships (Goldstein, 1987; Schiffman et al., 2002; Morrison, 2003), an urban upbringing compared to rural environments (van Os, 2004), being part of an ethnic minority or an immigrant (Kirkbride et al., 2008) have all been associated with greater risk for schizophrenia. Education level, income, family history of substance abuse disorders or harmful substance use, smoking, starting age and frequency of cannabis use can also act as predictors of schizotypy scores (Eren et al., 2017).

1.3.3 Neurotransmitters

Numerous neurotransmitters and pathways have been suggested as having a role in the aetiology of schizophrenia. Difficulties arise in appraising single systems due to the numerous complex interactions between neurotransmitter systems. Historically and to date the most predominantly implicated neurotransmitter system in schizophrenia is the dopaminergic system. However, there are a number of findings that suggest the potential involvement of other neurotransmitters. There is a large variance in the effectiveness of antipsychotic D2 receptor antagonists (Mortimer et al., 2010; Kapur et al., 2000) with an estimated one third of individuals diagnosed with schizophrenia being unresponsive to antipsychotic drug treatment. Antipsychotics are also limited in their ability to improve negative or cognitive symptoms, with some even worsening symptoms (Kim et al., 2013; Murphy et al., 2006). The most recent evidence regarding dopamine in schizophrenia suggests it is limited to psychosis (Howes and Kapur, 2009). It is therefore important to research other potential neural substrates. Previously implicated systems include cannabinoid, serotonin, GABA and glutamate systems (Tandon et al., 2009). This study aimed to focus on
the potential role of cannabinoids in schizotypy, particularly in its effect on the different underlying components of schizotypy, schizotypy structure and as it relates to more established effects of dopamine.

1.4 The Cannabinoid Hypothesis

The Cannabinoid Hypothesis of schizophrenia posits that cannabis contributes towards the development of schizophrenia and associated symptoms. This hypothesis was initially conceived on two primary lines of evidence: epidemiological studies and the observable similarities in cannabis intoxication reports and psychotic symptoms of schizophrenia.

1.4.1 Epidemiology

Early epidemiological studies noted that there was a greater likelihood of current or previous cannabis use in people diagnosed with schizophrenia compared to the general population. Individuals who exhibited psychosis were more likely to report cannabis use in the past year (30%) compared to non-psychotic people (10%) (Degenhardt and Hall, 2001). In a studied sample, 25% of patients with schizophrenia were diagnosed with cannabis use disorder (Koskinen et al., 2009). However, there are also high levels of generalised substance abuse disorder among individuals with schizophrenia both in prodromal and first episode cases (Degenhardt and Hall, 2001). Indeed, schizophrenia has been associated with the increased use of a majority of drugs. Individuals with psychosis are more likely to heavily smoke tobacco cigarettes and use excessive amounts of stimulants and opioids than cannabis (Ksir and Hart, 2016) and while cannabis use may be associated with increasing severity of symptoms and risk of relapse in schizophrenia so are other drugs (Linszen et al., 1994; Baigent et al., 1995). On the other hand, some studies have found that cannabis use in recent onset psychosis does not appear to be associated with differences in either positive or
negative symptoms but was associated with higher levels of depression and anxiety (Barrowclough et al., 2015) as with the CB1 antagonist, rimonabant (Moreira and Crippa, 2009). Indeed, it is important to note that increased cannabis use is also associated with a number of other psychiatric disorders and illnesses such as depression (Patton et al., 2002) and bipolar disorder (Arendt et al., 2007). As such, epidemiological studies alone would suggest that it is more likely that there is a broad overarching relationship between psychiatric disorders and substance use not a specific association between cannabis use and schizophrenia.

1.4.2 Cannabis as a model of psychosis

Ames was the first to present cannabis as a model for psychosis over 50 years ago (Ames, 1954). In the following years many studies have noted the strong similarities between the induced subjective effects of cannabis and cannabinoid agonists with endogenous schizophrenic psychosis (Emrich et al., 1997; D'Souza et al., 2004). Both natural and synthetic cannabinoids have been seen to induce a wide range of transient and dose-related symptoms, that encompass the positive, negative and cognitive symptom dimensions associated with schizophrenia. Healthy individuals who use cannabis have reported psychotic symptoms such as perceptual and sensory distortions, anxiety, paranoia, body perception changes, derealization and depersonalisation (D’Souza et al., 2009). Cannabis has also induced negative symptoms including blunted affect, reduced rapport, decreased spontaneity and emotional withdrawal (D’Souza et al., 2009; Morrison and Stone, 2011). Observations of negative symptoms could potentially be confounded by the sedative effects of cannabis, however there is some evidence that THC-induced negative symptoms were not a result of any sedative or cataleptic effects (Morrison and Stone, 2011). In a study with healthy volunteers who received intravenous THC, schizophrenia-like negative symptoms were elicited, with those symptoms exhibiting no relationship to self-rated sedation (Morrison and
Schizophrenia-associated cognitive deficits are also observed under THC with dose-related impairments in working memory, recall and attention in healthy subjects, relatives of patients with schizophrenia and the patients themselves (Emrich et al., 1997; D'Souza et al., 2004).

1.4.3 Cannabinoids and Schizotypy

The exact relationship of cannabis and cannabinoids to schizotypy is unknown. A number of studies have shown correlations between cannabis use and positive, negative and disorganised schizotypal dimensions. Cannabis use has correlated with positive schizotypal symptoms (Davis et al., 2013) and people who use cannabis show higher schizotypy scores compared to non-users (Williams et al., 1996; Mass et al., 2001; Dumas et al., 2002) with individuals currently using cannabis displaying higher schizotypy scores than past users (Skosnik et al., 2001). Schizotypal personality scores and magical thinking are higher in subjects that have a history of cannabis use compared to those who do not (Dumas et al., 2002). Schizotypal symptoms of perceptual deviations, magical thinking and anxiety have been observed under the effect of cannabis (Keeler et al., 1971). Other studies have found that while people who use cannabis did not have higher schizotypy scores, a greater frequency of cannabis use was associated with higher measures of schizotypy (Stirling et al., 2008). Cannabis use has been observed to correlate with specific schizotypal traits in healthy subjects which may indicate that there is a correlation between cannabis use and personality dimensions that reflect a psychosis proneness in healthy subjects (Williams et al., 1996). Any possible causal relationship(s) underlying these associations are unclear. Are people with high schizotypy more prone to cannabis use? Does chronic cannabis use increase schizotypy? Is cannabis use in those with high schizotypy due to self-medication? There is evidence of cannabis use relating to lower negative schizotypal symptoms (Davis et al., 2013) or acting as an anti-psychotic (Schwarcz et al., 2009), which would support the idea of cannabis as a form
of self-medication. On the other hand, the association may be neither psychologically or pharmacologically specific. For example, people with high schizotypy may also be high in anxiety and/or depression and the association with cannabis may be related to those measures. A more general model and alternative explanation is substance use to alleviate dysphoria. This model suggests that individuals with severe mental illnesses, such as schizophrenia or psychotic disorders, are prone to feelings of dysphoria, with substance use an effort to mitigate these feelings (Mueser et al., 1998). There is also a significant association between pre-existing mental disorders and an increased risk of developing a substance use disorder (Marel et al., 2016). People high in schizotypy and/or anxiety etc., may just be prone to increased substance use, and cannabis is just one of the most common substances used (Mueser et al., 1998; Marel et al., 2016). Finally, the association may be due to all of the above, varying across individuals.

1.4.3.1 Self-Medication Hypothesis

Cannabis as a form of self-medication was originally conceived on the basis of self-reports from psychotic patients (Dixon et al., 1990). It has been argued that cannabis use in schizophrenia may reflect efforts to mitigate aversive symptoms or to counteract side effects associated with antipsychotic treatment (Verdoux et al., 2005). In support of this hypothesis were two studies which administered Dronabinol (synthetic Δ9-Tetrahydrocannabinol) to people with schizophrenia and 8/16 people reported significant reductions of psychotic symptoms, with decreased hallucinations, thought disorder and conceptual disorganisation (Schwarz et al., 2009, 2010). It is important to note that in these studies participants were patients who had exhibited previous improvements with cannabis use, which along with the small sample size and open-label nature of the study may have affected the results. Currently there is insufficient evidence, epidemiologically or mechanistically, to compellingly argue that cannabis has an anti-psychotic effect or is used as a form of self-medication. More
research is required, with a broad scope of schizotypy components to assess the possible role of CB1 receptor agonists as potential antipsychotics.

1.4.4 Pharmacology

- Cannabis consists of two primary constituents: Δ9-Tetrahyrdrocannabinol (Δ9-THC) and Cannabidiol (CBD). Δ9-THC is the main psychoactive component and is a partial agonist at both CB1 and CB2 receptors with low intrinsic activity (Selley et al., 1996) and a high affinity (Martin et al., 1999) at the receptors. CB1 receptors are thought to be the most expressed G-protein coupled receptor in the CNS (Breivogel and Childers, 1998). CB1 receptors are widely expressed and appear in relatively high densities in the following regions listed from highest to lower density: Substantia nigra pars reticulata, Globus pallidus internal segment, Globus Pallidus external segment, putamen, molecular layer of dentate gyrus, cingulate gyrus, caudate, basolateral amygdala, hippocampal layer CA1, molecular layer of cerebellum and medial hypothalamus, central grey. These regions, particularly the first six, have been previously implicated as potential neural substrates for psychosis. CB1 receptors are predominantly located presynaptically and localized to axons and nerve terminals and can modulate presynaptic regulation of neurotransmitter release (Irving et al., 2008; Freund et al., 2003). Primarily expressed on the terminals of GABA and glutamate containing neurons (Katona et al, 1999; Chevalleyre et al., 2006), stimulated CB1 receptors have been seen to inhibit presynaptic glutamate and GABA (Matyas et al., 2008; Tzavara et al., 2003). There are reports of CB1 receptor interactions regarding the release of other neurotransmitters, especially acetylcholine (Acquas et al., 2000). However, direct effects have rarely been established, and there is a strong possibility effects could be indirect or secondary to the modulation of glutamate or GABA release. For example, there is no mRNA for CB1 receptors in dopamine neurons and
no evidence of direct effects of CB1 receptors on dopamine activity, yet there is some
evidence that supports CB1 receptor activation can increase (Malone and Taylor,
1999), decrease (Cadogan et al., 1997) or have no effect on (Kofalvi et al., 2005),
dopamine release (for a discussion of the implication of these findings, see Section
1.5.2).

1.5 The Dopamine Hypothesis

The dopamine hypothesis was conceived upon the convergence of a number of
findings. The first was that Reserpine, which blocks the vesicular monoamine transporter
Type 2 and subsequently stopping the movement of monoamines was effective in the
improvement of acute psychotic symptoms (Carlsson et al., 1957), although this may have
been due to effects on noradrenaline, dopamine or serotonin. The second was that
antipsychotic drugs increased dopamine metabolism (due to increased release of dopamine)
in animal studies (Carlsson and Lindqvist, 1963). Clinicians had observed that
amphetamines, which increase synaptic monoamine levels, could induce acute psychotic
symptoms (Connell, 1957), and experimental studies in healthy volunteers without
psychiatric illness confirmed this (Angrist and Gershon, 1970; Angrist et al., 1974;
Kokkinidis and Anisman, 1981). The average clinical dose of antipsychotic drugs is highly
correlated to dopamine D2 (but not D1) receptor affinity (Seeman et al., 1976; Creese et al.,
1976). All current antipsychotic drugs used in schizophrenia reduce dopamine transmission at
the D2 receptors, either as antagonists, inverse agonists, or partial agonists1. Together, these
discoveries led to the theory that psychotic symptoms were due to hyperactive dopamine

1 There is one antipsychotic medication, pimavanserin, specifically for people with Parkinson’s disease in which
disease dopamine cells are mostly dead, that does not have direct dopamine effects but rather affects 5-
hydroxytryptamine receptors (Stahl, 2016).
function and in turn centred dopamine as the primary neurochemical area of interest in schizophrenia research.

Davis et al. (1991) elaborated upon this initial theory proposing a regionally specific prefrontal hypodopaminergia and subcortical hyperdopaminergia. It was suggested that dopamine abnormalities in specific brain regions corresponded to specific symptoms of schizophrenia; striatal hyperdopaminergia with positive symptoms and frontal hypodopaminergia linked to negative symptoms. Although more complex than the first dopamine theory, there were a number of limitations in this version. There was a large reliance upon inferences from animal models and a lack of direct evidence regarding low dopamine levels in the central cortex. However, a recent Positron Emission Tomography (PET) study supports a decrease in dopamine release in the frontal cortex in drug-free and drug-naïve people with schizophrenia (Slifstein, 2015).

The most recent version of the dopamine hypothesis suggests that the interaction of multiple ‘hits’ result in dopamine dysregulation (Howes and Kapur, 2009). The location of this dysregulation was further specified to occur at presynaptic dopaminergic control levels and clarified to relate to psychosis specifically rather than schizophrenia generally. Radiolabeled L-DOPA studies showed elevated striatal dopamine synthesis capacity in schizophrenia (Reith et al., 1994; Abi-Dargham and Moore, 2003; Kumakura et al., 2007). There is increased amphetamine-stimulated DA release in people with schizophrenia compared to controls (Abi-Dargham, 1998; Abi-Dargham, 2009; Breier, 1997; Kegeles, 2000; Laruelle, 1998; Laruelle, 1996; Slifstein, 2010; Weinstein, 2018). People with schizophrenia had significantly elevated presynaptic dopamine availability during episodes of acute psychosis (Hietala et al., 1995; Howes et al., 2008; Lindstrom et al., 1999). SPECT and PET studies show evidence of almost doubled radiotracer displacement from dopamine receptors in individuals with schizophrenia compared to control groups. Patients with
Schizophrenia have also shown increased baseline occupancy of D2 receptors by dopamine (Abi-Dargham, 2000). Numerous meta-analyses of the role of D2/3 receptors (Kestler et al., 2001; Laruelle, 1998; Zakzanis and Hansen, 1997) concluded that (excluding effects of antipsychotics) there is at most a small (~10-20%) elevation in striatal D2/3 receptor density in patients, and the general consensus is that there are not changes in post-synaptic dopamine receptors in schizophrenia, but rather altered changes in release from the presynaptic terminals. This elevation appears to be regionally specific with no elevation outside of the largely defined striatum and specific to D2/3 receptors with no similar findings or changes reported in D1 receptors. However, it is worth noting that not all people with schizophrenia respond to D2 receptor medication (Mortimer et al., 2010), and that treatment unresponsiveness is associated with lack of increased dopamine synthesis (Kim et al., 2017).

Evidence for the role of dopamine in psychosis is substantive, but more research is required to better understand the extent of influence dopamine plays in various subtypes of schizophrenia, exact mechanisms and potential for more effective treatments.

1.5.1 Schizotypy and dopamine

Studies of the association between dopamine and schizotypy reflect those observed in schizophrenia to an extent. There is evidence that with increased striatal dopamine release there are following effects on schizotypy (Woodward, Cowna and Park., 2011; Kegeles, 2004). There is also substantial evidence from behavioural studies that show high levels of schizotypy (predominantly positive dimensions) have been associated with dopamine-sensitive functions. In contrast, there has also been evidence of no association between elevated striatal dopamine release and schizotypy measures (Thompson and Rosell, 2020) and potential differential association of dopamine with different dimensions of schizotypy. One PET study found no association of dopamine release in the striatum with schizotypal personality disorder but did find a small positive correlation between dopamine release and
cognitive-perceptual symptoms in the ventral striatum (Thompson and Rosell, 2020). This could support the current Dopamine Hypothesis emphasis on the role of dopamine exclusively in the expression of “psychosis” as opposed to a relationship to schizotypy, or schizophrenia.

1.5.2 Cannabinoids and Dopamine

It has been argued that the observed psychomimetic effects of cannabis may be mediated by an enhancement of, or interaction with, the dopaminergic system. Previous studies regarding cannabinoids and dopamine release have been mixed. There is some evidence indicating that cannabinoids increase dopamine release (Malone and Taylor, 1999) cannabis decreases dopamine release (Cadogan et al., 1997) or have no effects (Barkus et al., 2011; Szabo et al., 1999; Köfalvi et al., 2005). A PET study by Bossong et al (2009, 2015) observed significantly increased dopamine release (reduced binding of raclopride, a dopamine D2/D3 receptor tracer in the ventral striatum, pericommissural dorsal putamen after inhaled THC compared to placebo, suggesting increased release of endogenous dopamine in these areas. However, the sample size was very small, and the region is also small, limiting the sensitivity of the PET studies. Similarly, significant increases in dopamine release (decreases in cortical binding of radiolabelled raclopride in the cortex) after THC has also been observed (Stokes et al., 2010), which is the opposite effect reported for people with schizophrenia (Slifstein, 2010). A PET study in people who chronically use cannabis and experience psychosis indicated a reduction in dopamine release in the striatum (Bloomfield, 2014). Some studies have found no significant difference in dopamine release after THC even with the presence of psychotic indicators (Barkus et al., 2011). Other studies have observed cannabinoid-induced decreases in dopamine release with inhibitions of the second-messenger systems activated by dopamine D1 receptors (Cadogan et al., 1997). There is no evidence of CB1 receptors on dopamine neurons, and in striatal slices CB1 agonists had no
effect on dopamine release (Kőfalvi et al., 2005). However, there is evidence of CB1 receptors inhibiting both glutamate (Melis et al., 2004) and GABA (Mátyás et al., 2008) release in the Ventral Tegmental Area (VTA) altering the excitation and inhibition of dopamine neurons. Most commonly observed is an increase in neuronal firing with subsequent increases in dopamine release at downstream forebrain regions (Melis et al., 2004; Barkus et al., 2011). The possibility of secondary or downstream effects means it is unclear what the net effect CB1 activation could have on dopamine release and is a potential explanation for the contradictory reports.

1.6 Drug Challenges

Short-term drug application can directly modulate neural systems, allowing for the evaluation of potential acute neurotransmitter effects on different domains and insight into possible neural correlates.

1.6.1 Nabilone

Nabilone (Cesamet®) is an orally active synthetic cannabinoid agonist of similar chemical structure to Δ⁹-THC. Clinically it is used as an antiemetic in the management of chemotherapy-induced nausea and vomiting in treatment resistant patients (MEDA Pharmaceuticals, 2013). Like THC, Nabilone is a partial agonist at CB1 and CB2 receptors but has around 5x greater affinity and 2x greater biological activity (National Centre for Biotechnology Information (2019)). Nabilone also has a more rapid and dependable absorption into the gastrointestinal tract (Karschner et al., 2011). Nabilone exhibits peak plasma concentration approximately 2.0 hours after administration of a 2 mg dose, with a half-life of approximately 2 – 3.5 hours (Lemberger et al., 1982; MEDA Pharmaceuticals, 2013). Nabilone has previously induced subjective and cognitive effects similar to those observed under marijuana (Kalant, 2004; Wesnes et al., 2010), with comparable subject self-
reported drug effects to those induced by Δ9-THC (Lile et al., 2010). In drug discrimination procedures, it has been found to fully substitute for Δ9-THC (Lile et al., 2010). Effects reported by clinicians include dizziness, drowsiness, euphoria, ataxia, anxiety, disorientation, depression, hallucinations and psychosis (Wesnes et al., 2010), although there is no comparison with the incidence after placebo, causality has not been determined.

Administration of a standard prescription of 2 mg results in impairments in psychomotor speed, attention and working and episodic memory, and dose-dependent impairments in cognition between 1-3 mg, with increasing dose leading to increased impairments (Wesnes et al., 2010). Nabilone has also resulted in feelings of panic, fear and paranoia, loss of control, thought disturbances, feelings of unreality, apprehension, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucination and other perceptual alterations. As Nabilone fits the pharmacological profile of Δ9-THC, is available for prescription in Australia and in clinical studies has proven to result in similar subjective effects as cannabis it was determined to be a suitable testing model for this study.

1.6.2 DEX

Dexamphetamine (DEX), or C⁹H¹³N, is a dextro-enantiomer of amphetamine with a similar chemical structure to catecholamine neurotransmitters such as dopamine. It is a psychostimulant that is used clinically in the treatment and management a broad range of disorders including ADHD, narcolepsy, obesity, parkinsonism and traumatic brain injury (Heal et al., 2013). It reverses the direction of noradrenaline and dopamine transporters, as in the case of dopamine, the DAT, leading to increased neurotransmitter release into the synapse (Sulzer et al., 2005). Amphetamine also has an affinity for VMAT2, preventing the translocation of dopamine into intraneuronal storage vesicles, resulting in elevated intrasynaptic dopamine levels (Sulzer et al., 2005; Kahlig et al., 2005; Heal et al., 2013) available for release. Amphetamines induce psychosis-like symptoms that are dependent on
dose, duration and the susceptibility of the subject (Lieberman et al., 1987; Abi-Dargham et al., 2004). The doses of dexamphetamine that induced psychosis in healthy volunteers were between 270-520 mg (Angrist, 1971). In individuals with schizophrenia, there is greater amphetamine induced dopamine release compared to controls, with the severity of psychotic symptoms correlated to the magnitude of dopamine release (Heal et al., 2013). Amphetamine-induced striatal dopamine release is also seen to be increased in Schizotypal Personality Disorder (Kühn et al., 2012; Hazlett et al., 2012; Ettinger at al., 2014), though to a smaller degree than observed in schizophrenia (Abi-Dargham et al., 2004). Prior studies have shown that Dexamphetamine significantly increases schizotypy scores in healthy volunteers, measured by the assessment such as the Brief Psychiatric Rating Scale Extended Version (BPRS-E), Launay-Slade Score (LSHS-R) and Assessment of Positive Symptoms Scale (SAPS) (Loffman et al., 2017). There has been little research into the effect of DEX on individual schizotypal components which may provide more information on potential role for dopamine in specific underlying aspects of schizotypy.

1.7 Illusions and Hallucinations

Illusions are misperceptions of real stimuli. Hallucinations in comparison are perceptual aberrations in the absence of external stimuli. Both, however, involve anomalies of perception, which has been linked to prodromal psychosis (Yung and McGorry, 1996). Studies that have investigated the potential strength of illusions in schizophrenia have resulted in mixed findings. Some studies have found significantly increased illusion perception in schizophrenia patients (Capozzoli and Marsh, 1994; Tam et al., 1998; Kantrowitz et al., 2009; Chen et al., 2011) while other studies have reported weaker illusion perception (Emrich et al., 1997; Tadin et al., 2006; Keane et al., 2013; Yang et al., 2013). Different illusions of different modalities present contradictory results. Even in the case of
the same illusions results have differed (Tibber et al., 2013; Yang et al., 2013). These contradictions could be due to the majority of these studies using small sample sizes leading to insufficient statistical power. It has been proposed that the hallucinations could be the illusion of reality, meaning that illusion related processing may offer an avenue of insight into the studying of hallucination substrates.

In schizophrenia auditory hallucinations are the most common hallucination, occurring in approximately 74% of diagnosed individuals (Sartorius et al., 1974). Event-related potential studies that utilized the Deutsch ‘High’ or ‘Low’ word illusion indicate that the illusion tigered a dynamic cerebral response that was similar those observed in auditory verbal hallucinations (Xu et al., 2016). Research into the potential role of dopamine in the Deutsch Phantom Word illusion demonstrated that DEX increased illusory experience with a greater number of phantom words heard compared to placebo (Loffman et al., 2017). Utilizing Illusions as a measure of perceptual anomalies and a possible indicator of auditory hallucination vulnerability it may be possible to further explore the role of cannabinoids and dopamine in hallucination expression within schizophrenia.

1.8 Objectives, Aims, and Hypotheses

The severe individual and broader societal consequences of schizophrenia, combined with the high and increasing prevalence of cannabis use, make gaining further insight into potential associations between cannabis and schizophrenia important. Furthermore, with current limitations of antipsychotic medications, correlations with negative symptoms, and overall poor treatment outcomes, the discovery of potential treatments is important. However, research is often limited by a number of factors including the heterogenous expression of schizophrenia and a multitude of confounds including medication, comorbid symptoms and relatively low prevalence. Medication is particularly relevant as it is difficult to determine a
schizophrenia symptom profile based on increased dopamine release when dopamine antagonists are present in the system. A strategy to bypass some of these issues is to utilise schizotypy as a model for schizophrenia. This allows for the investigation of schizophrenia-like psychopathology in healthy volunteers. A greater understanding of schizotypy may lead to a better understanding of the underlying aetiology, potential risk factors and lead to the development of improved treatments and prevention. As schizophrenia has been linked to a number of psychiatric comorbidities it can also assist in studying the expression of linked disorders such as anxiety and depression. The aim of this study was to use a pharmacological challenge of Nabilone, a synthetic THC analogue, to explore the association between cannabis and schizotypy. Further, comparing Nabilone results with those attained in a previous study of DEX, including a factor analysis to assess underlying dimensional structures of drug effects, could provide a better understanding of respective roles and effects of cannabinoids and dopamine in schizophrenia. Past research into the potential interaction of cannabis, cannabinoids and schizophrenia has been mixed at best. Studies have not provided clear evidence of the effect of CB1 agonists on schizotypy with widespread discrepancies and contradictions. This could potentially be due to different methodology, sample groups and limited sample sizes or individual differences. However, there have also been few studies that have focused on the analysis of underlying schizotypal components (Davis et al., 2013). Due to the mixed nature of previous reports regarding the observable and subjective effects of cannabinoid agonists, this study aimed to test the competing hypotheses that (1) Nabilone and DEX would affect different schizotypal components and dimensions; (2) Nabilone and DEX would have similar effects on schizotypal components and dimensions; (3) Nabilone would decreases the schizotypal components that DEX increased; (4) unlike DEX, Nabilone would not affect schizotypy.
2. Methods

2.1 Nabilone Study

2.1.1 Ethics approval

Ethics approval was obtained from the University of Western Australia Ethics Committee (RA/4/20/4558) and the trial was registered with the ANZ Clinical Trials Registry (ACTRN12618001292268), and the Therapeutic Goods Administration (TGA Clinical Trial Repository CT-2018-CTN-02561-1). Professor Mathew Martin-Iverson held a Schedule 8 permit for Nabilone, and Professor Joseph Lee was the Authorised Prescriber and Dispenser.

2.1.2 Recruitment and Incentives

Recruitment occurred via personal invitations from investigators, approved advertisements during University of Western Australia (UWA) Pharmacology Lectures, posters placed around campus and via social media posts on Facebook and Reddit. No financial incentive was offered for participation; however, participants were provided breakfast, lunch and transportation to and from testing.

2.1.3 Participants

To be considered eligible participants had to be of sound health, not currently taking any medication (excluding contraceptives and acne medication) and between the ages of 18 and 60. Prior to participation, participants were required to undergo a comprehensive psychiatric and medical screening by a psychiatrist to ensure suitability. Twenty-four healthy volunteers (14 male and 10 female) aged 18 to 57 participated in the study. The average age of participants who completed the study was 26.46 years old with a range of 19 to 57 and standard deviation of 7.79 years.
Initially all participants were to receive 2 mg Nabilone (PO, bid, n=4), based on the standard clinical prescription as an anti-emetic. On the 2 mg dose, four of the first eight participants reported adverse effects including nausea, emesis, orthostatic hypotension and/or syncope and were therefore removed from the study prior to completion. Subsequently, dosage was reduced to 1 mg Nabilone (PO, bid, n=21) after which one further participant reported an adverse response and did not complete testing.

2.2 Dexamphetamine Study

The DEX study was completed in the same laboratory two years prior by Mark Lim and Sean Loffman with assistance from Sophie Slawik and Katharina Gauss. Twenty healthy volunteers (15 male, 5 female) ranging from 18-27 years old were recruited via investigator invitations, lecture advertisements and posters. DEX dosages were calculated based on participant weight at 0.45 mg/kg with the mean weight of participants 72.02 kg and mean DEX dosage 32.41 mg. General procedures were mostly identical to those followed in the Nabilone study, with the exception of only a single admission of the MIS, PAS, LSHS-R, BPRS-E and SAPS questionnaires per testing day. The MTB and AMQ were also completed 5 times each testing day instead of 7. There was no inclusion of the ARCI-MMQ scales which were introduced in the Nabilone study. Data from this study was drawn from the original physical participant files and re-entered and analysed for this experiment.

2.3 General Procedures

This study was a within-subject, double-blind, placebo-controlled and drug-order balanced crossover trial. Drug order was balanced with permuted block randomisation. Participants completed two full testing days (one day on placebo and one day on Nabilone), separated by a minimum seven-day washout period. Prior to starting participants were provided a study information form, a pharmaceutical information form on Nabilone and were
asked to sign a consent form (see Appendix). Participants then completed a demographic information form and previous substance use form. Both testing days followed an identical structure and timetable with consistent investigators present at each task. The first capsule of Nabilone or placebo was given following the completion of the initial demographic forms. Participants then had a 45-minute period of rest and a 25-minute break for breakfast, allowing for a total of 70 minutes for absorption of the drug prior to testing. Participants then completed a number of tests including working memory digit span and spatial span tests, and sensory illusions tests. The second capsule was administered a minimum of 3.5 hours following the first dose. Participants continued with testing after the second dose, including the Phantom Words Illusion test. At the end of each testing session participants were required to pass an end-of-day questionnaire that ensured it was safe for them to leave the supervision of the investigators and return home in the company of a responsible adult.

2.4 Materials and Questionnaires

2.4.1 Schizotypy Questionnaires

The questionnaires used to assess schizotypy included a selection of self-report and investigator observation-based scales. These included the BPRS-E, MIS, LSHS-R, PAS, and SAPS. These questionnaires had been used in the 2017 DEX study and so were readministered in the Nabilone study for continuity and to allow for a direct comparison of results. During each testing session the schizotypy measures were completed twice, approximately 2 hours after each capsule which was estimated to be the time of peak drug effect based on Nabilone pharmacological information and previous studies. Each item of each questionnaire was determined to correspond to a specific schizotypy component (see Appendix for marking keys). There was a total of twenty-six schizotypy components identified over all questionnaires.
2.4.1.1 Brief Psychiatric Rating Scale – Expanded (BPRS-E)

The BPRS-E (Lukoff et al., 1986) is a rapid assessment tool for major psychiatric characteristics used by researchers and clinicians. It consists of 24 items, 14 based on answers to interview questions and 10 on observations of behaviour by the interviewer. Items are rated from Not Assessed (NA) to Extremely Severe (7), with a possible score range of 0 to 168. Interview questions relate to different items such as anxiety (‘Have you been worried a lot during today?’), depression (‘How has your mood been recently?’), guilt (‘Have you been thinking about past problems?’), grandiosity (‘Do you have any special abilities or powers?’) and disorientation (‘How old are you?’). With observation criteria including emotional reactivity, physical and motor manifestation, attention and co-operativeness. The BPRS-E has been found to be a psychometrically sufficient measure for rating the severity of psychopathology consistent with clinically derived symptoms (Thomas et al., 2004) and has a significant sensitivity to change (Burlingame et al., 2006). Compared to the BPRS, the BPRS-E covers a broader range of symptoms considered under schizophrenia and mood disorders including bizarre behaviour, self-neglect, distractibility, and elevated mood (Ventura et al., 1995).

2.4.1.2 Magical Ideation Scale (MIS)

The MIS scale assesses concepts of causation in comparison to conventional belief standards and magical ideation (Eckblad and Chapman, 1983). It is a self-rated measure that consists of 30 ‘True’ or ‘False’ items that each correspond to different items of magical thinking. Statements relate to components such as delusions of reference (‘Numbers like 13 and 7 have no special powers’), delusions of control (‘Some people can make me aware of them just by thinking about me’), thought insertion (‘I have never had the feeling that certain thoughts of mine really belonged to someone else’), mind reading (‘I have sometimes felt that strangers were reading my mind’) and persecutory delusions (‘The government refuses to tell
us the truth about flying saucers’). The psychometric properties of the MIS have been demonstrated in a number of studies and across a wide range of data (Chapman et al., 1995; Edell, 1995; Kwapis et al., 2008).

2.4.1.3 Perceptual Aberration Scale (PAS)

The PAS measures personal perceptual aberrations (Chapman, Chapman and Raulin, 1978). The PAS consists of 35 self-rated questions with ‘True’ or ‘False’ answers with a possible score range from 0-35. Questions relate to components such as somatic hallucinations (‘I have sometimes felt confused as to whether my body was really my own’), auditory hallucinations (‘My hearing is sometimes so sensitive that ordinary sounds become uncomfortable’), visual hallucinations (‘The indoor lights seem so bright today that they bother my eyes’) and somatic delusions (‘I have felt a thought my head or limbs were somehow not my own’). The psychometric properties of the PAS have been supported by a number of studies and across a wide range of data (Chapman et al., 1995; Edell, 1995; Kwapis et al., 2008).

2.4.1.4 Launay–Slade Hallucination Scale Revised (LSHS-R)

The LSHS-R is a self-rated measure of hallucinatory experiences in non-clinical populations (Waters et al., 2003). The LSHS-R consists of 12 true or false items with possible scores of 0-12 where a higher score reflects increased proneness to hallucinatory experiences. Statements relate to components such as auditory hallucinations (‘I have heard the voice of the devil’), visual hallucinations. (‘On occasions, I have seen a person’s face in front of me when no-one was in fact there’), persecutory delusions (‘Sometimes a passing thought will seem so real that it frightens me’) and delusions of reference (‘Sometimes my thoughts seem as real as actual events in my life’). The LSHS-R has been shown to have
sufficient psychometric properties including validity and reliability (Waters et al., 2003; Cella et al., 2008).

2.4.1.5 Scale Assessment of Positive Symptoms (SAPS)

The SAPS is a scale for positive psychotic symptoms of schizophrenia used in research and clinical settings. The SAPS contains 4 major groups of symptom classes (hallucinations, delusions, bizarre behaviour and thought disorder) each containing a number of subgroups, for a total of 24 items. Each component is scored from 0, or not present, to 5, or severe, with a total possible score range of 0-170. Scores are based on responses to the BPRS-E, MIS, LSHS-R, PAS, interview responses and investigator observations. The SAPS has shown to have consistent interrater reliability (Andreasen et al., 1991).

2.4.2 Mood Questionnaires

General mood and drug effect questionnaires were completed seven times throughout the day, right before the first dosage and then approximately 70, 90, 130, 240, 300 and 380 minutes afterwards.

2.4.2.1 Amphetamine Mood Questionnaire

The AMQ is a self-rated questionnaire that assesses similarity of subjective mood to amphetamine like or amphetamine opposite/withdrawal states (McKetin et al., 1999). Participants are asked to mark on a visual Likert scale (10cm line) to gauge their current subjective state to the specific items. Items are measured by how far the indicated mark is from the left-hand end of the line, or not present, to the right, or present. It is broken down to AMQ like effects which consists of 10 items, possible scores 0-100, and AMQ opposite/withdrawal effects, which has 9 items and possible scores of 0-90. A higher score is indicative of an increased presence of amphetamine like or opposite mood states.
2.4.2.2 Addiction Research Centre Marijuana Questionnaire (ARCI-MQ)

The ARCI-MQ consists of 40 ‘True’ or ‘False’ items drawn from the National Institute on Drug Abuse inventory (Haertzen, 1974). Items assess perceptual and subjective mood effects associated with cannabis use. Twenty-two items are scored for True, while the remaining 18 are reverse scored. Possible scores are 0 to 40 with a higher score indicating the presence of a similar subjective state as that associated with cannabis intoxication.

2.4.2.3 Marteau Bekker Self Evaluation Questionnaire (MTB)

The Marteau-Bekker scale consists of six self-rated items that relate to a participant’s current state of mood. It is a smaller version of the Spielberg State-Trait Anxiety Inventory (Marteau and Bekker, 1992). Each item is scored on four-point Likert scale from one, not at all, to very much at four. Each of the items can be classified as either anxiety present or anxiety absent with possible total score range from 6 – 24. The Marteau-Bekker scale has been shown to have internal consistency reliability and validity compared to the full form state-trait anxiety inventory and is sensitive to state fluctuations of anxiety (Marteau and Bekker, 1992; Tluczek et al., 2009).

2.5 Auditory Illusion

The Phantom Words Illusion (PWI) is a unimodal auditory illusion test (Deutsch, 2003) where participants are presented with word/phrase combinations. This study used 'High-Low' and 'Harvey'. Audio stimuli was stereophonically presented via headphones, with different tracks presented to each ear. One ear received the stimulus at 400 Hz while the other received it at 800 Hz. Audio tracks were also presented across five different interaural interstimulus intervals (ISIs) (220, 440, 660, 880, 1100 ms). The 'Harvey' track was played first followed by the 'High-Low' track. ISI conditions started at 220 ms ISI, before incrementally rising in pairs with intertrial intervals 2000 ms each. Participants were asked to
indicate and then speak aloud whenever they perceived a unique phantom word which was then recorded, both digitally via a Blue Yeti Pro USB microphone and manually by investigators. The experiment was run using LabVIEW 8.2 software via a Provida IT PROV0806 PC running Windows XP OS. Stimuli were presented via Sennheiser HD 25-1 headphones at 100 dB. Count and latency of responses were recorded via a Logitech Attack3 ATK3 joystick.

2.6 Statistical Analyses

Statistical Analysis was performed using R statistics software (Version 3.5.2) and R Studio (Version 1.1.463) with additional packages. QQ plots and sm density plots were used to assess normal distribution and determine if parametric or non-parametric statistical methods were suitable. The AMQ-O, AMQ-L, MTB and ARCI-MQ were determined to be normally distributed and as such analysed using repeated measures analysis of variance (ANOVA), with post hoc Exact Bonferroni corrected paired t-tests for pairwise comparisons. To determine the factor structure of schizotypy a Multiple Factor Analysis was run on the schizotypy component mean scores taken from across the BPRS-E, MIS, PAS, LSHS-R and SAPS. An MFA is a multivariate data analysis method that simultaneously considers multiple sets of variables in the extraction of underlying group structures of data sets. Two schizotypy components (uncooperativeness and delusions of jealousy) were excluded from the MFA as no participants scored on either and as such may have erroneously identified as a separate individual factor. Performance on the Phantom Word Illusion test was determined by the average words reported during the illusion. Drug effects were assessed using ANOVAs with exact Bonferroni corrected paired t-Tests for pairwise comparisons. Correlation with schizotypy dimensions were completed via spearman correlation tests.
3. Results

3.1 Schizotypy

3.1.1 Global Schizotypy

The BPRS-E, LSHS-R, PAS, MIS and SAPS individual item scores were first converted to z-scores. The converted z-scores were then used to form average scores for each of the schizotypy components across all questionnaires. An overall schizotypy score was then calculated as the mean score of all the tested schizotypy components. Nabilone had no significant difference on the frequency distribution of overall schizotypy scores ($p=0.095$, $n=20$, permutation test) indicating no significant effect on overall schizotypy. There was a significant DEX induced difference with changes in frequency distribution of global schizotypy responses ($p<0.001$, $n=20$, permutation test) (Figure 1).

![Figure 1. Effects of Nabilone and DEX on overall schizotypy scores.](image)

Overall schizotypy scores were measured as a mean of the 26 schizotypy components assessed across the BPRS-E, MIS, PAS, LSS and SAPS. Response Density is indicative of the frequency distribution of responses (A) Nabilone had no significant effect on overall schizotypy scores ($p=0.1$, $n=25$, permutation test) (B) DEX caused a significant increase in the distribution of overall schizotypy scores ($p<0.01$, $n=20$, permutation test).
3.2 Multiple Factor Analysis

To conduct the MFA, the corresponding questionnaires from Nabilone and DEX (BPRS-E, LSHS-R, MIS, PAS and SAPS) were combined into joint questionnaire data sets. Questionnaire item scores from all measures were then converted to z-scores and used to form mean schizotypy component scores across all questionnaires. An MFA was then run on the component scores, resulting in the identification of three dimensions that contributed to 45% of the total variance in schizotypy scores. Each dimension included a number of schizotypy components of varying contributions (Table 1).

Table 1. The MFA of Nabilone and DEX schizotypy component scores identified three primary underlying dimensions: Delusions and Hallucinations Dimension, Mania-like Dimension and Delusional Guilt Dimension. Percentage contributions of each dimension to the total variance in schizotypy scores with the eigenvalues and loadings of associated schizotypy components.

<table>
<thead>
<tr>
<th>MFA Dimension (%) Contribution</th>
<th>Delusions/Hallucinations (26%)</th>
<th>Mania-like (11%)</th>
<th>Delusional Guilt (7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCZ Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Delusions</td>
<td>0.838</td>
<td>0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>General Hallucinations</td>
<td>0.769</td>
<td>0.011</td>
<td>0.007</td>
</tr>
<tr>
<td>Delusions of Reference</td>
<td>0.607</td>
<td>0.005</td>
<td>0.018</td>
</tr>
<tr>
<td>Somatic Delusions</td>
<td>0.592</td>
<td>0.008</td>
<td>0.047</td>
</tr>
<tr>
<td>Persecutory Delusions</td>
<td>0.58</td>
<td>0.008</td>
<td>0.002</td>
</tr>
<tr>
<td>Somatic Hallucination</td>
<td>0.513</td>
<td>0.002</td>
<td>0.073</td>
</tr>
<tr>
<td>Delusions of Grandiosity</td>
<td>0.430</td>
<td>0.003</td>
<td>0.046</td>
</tr>
<tr>
<td>Thought Insertion</td>
<td>0.419</td>
<td>0.016</td>
<td>0.018</td>
</tr>
<tr>
<td>Delusions of Control</td>
<td>0.398</td>
<td>0.104</td>
<td>0.004</td>
</tr>
<tr>
<td>Mind Reading</td>
<td>0.360</td>
<td>0.009</td>
<td>0.075</td>
</tr>
<tr>
<td>Energy</td>
<td>&lt;.001</td>
<td>0.489</td>
<td>0.044</td>
</tr>
<tr>
<td>Bizarre</td>
<td>0.102</td>
<td>0.485</td>
<td>0.010</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.035</td>
<td>0.348</td>
<td>0.197</td>
</tr>
<tr>
<td>Guilt</td>
<td>0.054</td>
<td>&lt;.001</td>
<td>0.786</td>
</tr>
</tbody>
</table>
To calculate a single dimension score for each MFA identified dimension the associated underlying schizotypy components were isolated and combined by their respective ‘weights’, or MFA determined dimension loadings. Normal Distribution tests indicated that the data sets of each MFA dimension scores were not normally distributed. Therefore, different scores after drug minus those obtained after placebo were calculated and significance of drug effect determined by permutation tests.

3.2.1 First Dimension: Hallucinations and Delusions

The First MFA Dimension accounted for 26% of the total variance in schizotypy scores. Comprised predominantly of hallucinatory and delusional components it was termed the Hallucination and Delusion Dimension. General hallucinations and general delusions were the primary contributors followed by delusions of reference, somatic delusions, persecutory delusions and somatic hallucinations in rank order (Table 1). There was no significant effect of Nabilone \( (p=0.11, n=24, \text{ permutation test}) \) or significant effect of DEX \( (p=0.384, n=20, \text{ permutation test}) \) on response frequencies of this dimension (Figure 2.).

![Figure 2](image_url)

**Figure 2. Effects of Nabilone and DEX on response density of MFA Dimension 1 weighted scores.** Density is the frequency of response. Scores for Nabilone and DEX were calculated as different scores drug minus placebo. Normal scores reflect random data samples. (A) Nabilone induced no significant different on weighted scores of the first MFA dimension \( (p=0.11, n=24, \text{ permutation test}) \). (B) DEX also had no significant effect \( (p=0.384, n=20, \text{ permutation test}) \).
3.2.2 Second Dimension: Mania-like

The second dimension accounted for a further 11% of the total schizotypy variance and included components of energy, bizarre behaviour and euphoria. This was termed the Mania-like Dimension. Nabilone did not have a significant effect on the response frequencies of the Mania-like Dimension (n=24, p=0.13, permutation test). DEX did have a significant effect, with overall greater response frequencies at higher dimension scores (n=20, p<0.001, permutation test) (Figure 3).

3.2.3 Third Dimension: Delusional Guilt

The third dimension contributed a further 7.7% to the overall variance and was most significantly defined by delusions of guilt and named the Delusional Guilt Dimension. This dimension was significantly affected by Nabilone (n=24, p=0.03, permutation test) with DEX inciting no significant effect (n=20, p=0.077, permutation test) (Figure 4).

Figure 3. Nabilone and DEX effects on the frequency distribution of MFA Mania-like Dimension 2 weighted scores. MFA 2 Scores were weighted combination of associated schizotypy components. Density is the frequency of response and drug effects were different scores of drugs minus placebo. (A) Nabilone had no significant effect on MFA Mania-like Dimension scores (p=0.13, n=24, permutation test) while (B) DEX did exhibit a significant effect (p<0.001, n=20, permutation test).
Mood Questionnaires

The data for the MTB, AMQ-L and AMQ-O subscales in both the Nabilone and DEX studies, and the MRCI-Q in the Nabilone study were determined to be normally distributed and as such repeated measures analysis of variance (ANOVA), with post hoc Exact Bonferroni corrected paired t-Tests were used for pairwise comparisons between drug and placebo. As mood questionnaires were completed at numerous intervals across each testing session, the effect of time was also assessed.

3.3.1 AMQ-L

Nabilone had no significant effect on the AMQ-L ratings \( F(1, 23) = 3.92, p = 0.06, \eta^2_G = 0.087 \) and no significant drug by time interaction \( F(1, 23) = 0.25, p = 0.62, \eta^2_G = 0.001 \). There was a significant effect of time itself \( F(6, 144) = 6.69, p = 0.017, \eta^2_G = 0.081 \). Dexamphetamine did have a significant effect on overall AMQ-L ratings \( F(1, 19) = 10.21, p = 0.0048, \eta^2_G = \)
and there was a significant drug by time interaction \( (F(4, 76) = 5.1, p < 0.001, \eta^G2 = 0.028) \) and effect of time itself \( (F(4, 76) = 8.52, p < 0.001, \eta^G2 = 0.035) \) (Figure 5).

3.3.2 AMQ-O

There was a significant effect of Nabilone on AMQ-O ratings \( (F(1, 23) = 4.44, p = 0.046, \eta^G2 = 0.086) \) with a significant drug by time interaction \( (F(6, 144) = 4.97, p = 0.036, \eta^G2 = 0.04) \). There was no significant effect of time by itself \( (F(6, 144) = 0.97, p = 0.33, \eta^G2 = 0.013) \). Dexamphetamine had no significant effect on AMQ-O ratings \( (F(1, 19) = 0.048, p = 0.83, \eta^G2 = 0.00021) \) however there was a significant drug by time interaction \( (F(4, 76) = 3.27, p = 0.016, \eta^G2 = 0.017) \) and significant effect of time \( (F(4, 76) = 3.73, p = 0.008, \eta^G2 = 0.029) \) (Figure 5).

3.3.3 MTB Anxiety

There was no significant effect of Nabilone on MTB ratings \( (F(1, 24) = 0.031, p = 0.86, \eta^G2 = 0.00018) \), no significant drug by time interaction \( (F(6, 144) = 1.25, p = 0.28, \eta^G2 = 0.006) \) nor effect of time by itself \( (F(6, 144) = 0.57, p = 0.76, \eta^G2 = 0.003) \). Dexamphetamine had a significant effect on MTB ratings \( (F(1, 19) = 4.99, p = 0.038, \eta^G2 = 0.031) \) however there was no significant drug by time interaction \( (F(4, 76) = 1.63, p = 0.17, \eta^G2 = 0.012) \) or effect of time \( (F(4, 76) = 0.71, p = 0.22, \eta^G2 = 0.034) \).

3.3.4 MRCI-Q

Nabilone caused significant increases in MRCI-Q scores compared to placebo \( (F(1, 19), p = 0.014, \eta^G2 = 0.086) \) with a significant effect of time \( (F(1, 19), p = 0.03, \eta^G2 = 0.081) \) but no significant drug x time interaction \( (F(1, 19), p = 0.24, \eta^G2 = 0.034) \).
Figure 5. Effects of Nabilone and DEX on the Amphetamine Questionnaire Subscales over time. The AMQ-L subscale indicated the presence of amphetamine like mood states and the AMQ-O subscale indicated the presence of amphetamine opposite or withdrawal mood states (A) Nabilone produced no significant effect on AMQ-L scores compared to placebo (n=24, p=0.06) (B) DEX caused a significant increase of AMQ-L scores (n=20, p<0.005) with a significant drug by time interaction (p<0.001). (C) Nabilone produced significant increases in AMQ-O scores (p=0.046) with a significant drug x time interaction (p=0.016) (D) DEX had no significant effect on AMQ-O scores (p=0.83).
3.4 Phantom Word Illusion

3.4.1 Nabilone and DEX effect

To assess the Phantom Word Illusion a mean word count over all ISI’s was calculated for Nabilone, DEX and respective placebo conditions. Nabilone had no significant effect on the overall Word count in the Phantom Word Illusion ($n=24, p=0.069$) while DEX did cause a significant increase in overall word count within the illusion ($n=20, p<0.05$) (Figure 7).

3.4.2 Correlation with Schizotypy

Difference scores of drugs minus placebo were calculated for the word count in Phantom Word Illusion in both the Nabilone and DEX studies. Different scores were then calculated for schizotypy, both overall scores and individual scores for each MFA identified dimension across both drug groups. Spearman correlation tests were then used to assess possible correlations between Phantom Word Illusion performance, as determined by word
count, and schizotypy measures. Spearman Correlation tests indicated that there was no significant correlation between overall schizotypy and word count in the Phantom Word Illusion for either Nabilone ($rs = 0.13, p = 0.53$) or DEX ($rs = 0.13, p = 0.53$). Neither Nabilone, nor DEX exhibited any significant correlations between word count and the identified schizotypy dimensions (Table 2).

![Bar Plots of mean word count in the Phantom Word Illusion for DEX and Nabilone compared to Placebo.](image)

**Figure 7** Bar Plots of mean word count in the Phantom Word Illusion for DEX and Nabilone compared to Placebo. Administration of DEX resulted in significant increases ($n=20, p=0.069$) in words reported compared to placebo condition. Nabilone did not have a significant main effect on the number of words reported ($p>0.05, n=25$).

**Table 2. Correlations between word count in the Phantom Word Illusion and the MFA identified schizotypy dimensions.** There were no significant correlations between Delusions/Hallucinations, Mania-like and Delusional Guilt dimensions and word count for either Nabilone or DEX.

<table>
<thead>
<tr>
<th>MFA Dimension</th>
<th>Delusions/Hallucinations</th>
<th>Mania-like</th>
<th>Delusional Guilt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$rs$</td>
<td>$p$</td>
<td>$rs$</td>
</tr>
<tr>
<td>Nabilone</td>
<td>0.1</td>
<td>0.53</td>
<td>-0.11</td>
</tr>
<tr>
<td>DEX</td>
<td>0.1</td>
<td>0.69</td>
<td>-0.02</td>
</tr>
</tbody>
</table>
4. Discussion

4.1 Summary of Results

This study used Nabilone, a synthetic THC analogue, to investigate the potential effects of CB receptor agonists on underlying schizotypy components in a non-clinical sample of healthy volunteers. These effects were compared to a previously conducted DEX study to investigate the potential respective effects, roles or interactions of cannabinoids and dopamine within schizotypy. Insight into these effects may help to improve understanding regarding the underlying factors of schizophrenic like psychopathology and therefore schizophrenia itself. The results of this study indicated that Nabilone and DEX had different effects on overall schizotypy, underlying schizotypy components and associated mood and drug states. Nabilone had no significant effect on overall average schizotypy scores while DEX induced significant increases in overall schizotypy expression. Combined Nabilone and DEX data identified three underlying dimensions of schizotypy: Hallucination and Delusion Dimension, Mania-like Dimension and the Delusional Guilt Dimension. Nabilone significantly increased the Delusional Guilt Dimension scores but had no significant impact on the other two dimensions. In turn, DEX incited significant increases in the Mania-like Dimension but had no significant effect on the other two dimensions. DEX also significantly increased mean word count in The Phantom Word Illusion, while Nabilone had no significant effect. Nabilone resulted in significant increases in AMQ-O scores and MRCI-Q scores but had no significant effects on the AMQ-L subscale or MTB anxiety scores. In contrast, DEX resulted in increases of the AMQ-L subscale and MTB anxiety scores with no significant effect on AMQ-O subscale.
4.2 Overall Schizotypy

4.2.1 Nabilone and overall schizotypy

The absence of a significant effect of Nabilone on overall schizotypy may suggest that the acute administration of a CB receptor agonist does not result in the significant expression of a schizotypy-like states. There have been some previous studies which also found no significant relation between cannabis use and schizotypy scores (Stirling et al., 2008). It does not necessarily align with previous evidence of cannabinoids causing acute and transient effects that would be considered schizotypal or psychomimetic. However, it is important to consider that in many of these studies effects occurred on an individual basis and were dose-dependent (Wesnes et al., 2010; D'Souza et al., 2004; D’Souza et al., 2009). Individuals with a psychiatric illness and or first degree relatives with a psychotic illness were specifically excluded, thus excluding those with a stronger propensity towards psychosis. The heterogenous nature of response and individual variation in cannabis effects are well established with evidence for individual differential sensitivity in regard to THC responses. Acute administration of THC has resulted in the formation of transiently psychotic and non-psychotic groups that exhibited significant differences in schizotypy scores, mood, anxiety and intoxication (Atakan et al., 2013). Patterns of differential sensitivity can extend to high and low doses of THC (Kirk and de Wit, 1999). Low dose THC has been observed to produce subjective stress-relieving effects while higher doses may non-specifically increase negative mood (Childs, 2019). Individuals who are at a risk of psychosis exhibit greater sensitivity to THC (Kuepper et al., 2001) as do patients with psychosis (Van Os et al., 2002; Henquet et al., 2005), and those are excluded from this study. Non-users typically report greater negative, cognitive or behavioural impairments compared to frequent users who may have lower negative expectations. Environmental, contextual and expectancy effects have also been observed to have a strong influence on outcomes of acute cannabis use.
Cumulatively this would suggest that there is a strong variability in THC or cannabis response, which in a study with a limited sample size as is the case of this trial, means that potential patterns, be they positive, negative or no effect may be unable to be appropriately identified.

4.2.2 DEX and overall schizotypy

DEX resulted in the significant increase of overall schizotypy scores. This effect mostly aligns with previous evidence regarding amphetamine type stimulants, and subsequent increases in striatal dopamine, and schizotypy (Woodward et al., 2011; Abi-Dargham et al., 2004; Kegeles, 2004). However, the most recent version of the dopamine hypothesis and current evidence regarding the role of dopamine links it’s role to the expression of psychosis specifically as opposed to schizophrenia, or schizotypy, generally (Howes and Kapur, 2009). One possible explanation is that while the overall schizotypy score determined in this study utilised a range of schizotypy components, a majority of components fell into the bracket of “positive” symptoms or those classically conceived of as “psychotic”. These results would suggest that increased dopamine levels, as induced by DEX, led to the expression of schizophrenia like traits and states.

4.3 Underlying Schizotypy Structure

The MFA determined that there were three underlying dimensions that contributed to majority of the total variance in schizotypy scores across the Nabilone and DEX populations: The Hallucination and Delusion Dimension, the Mania-like Dimension and the Delusional Guilt Dimension.

4.3.1 Hallucination and Delusion Dimension

The Hallucination and Delusion Dimension was formed from general hallucinations, general delusions, delusions of reference, somatic delusions, persecutory delusions, somatic
hallucinations, delusions of grandiosity, thought insertion and delusions of control in rank order of contribution. The presence of delusions, hallucinations and thought disorders reflect the classical positive dimension most commonly referenced in schizotypy and schizophrenia (Randrup and Munkvad, 1972; Fusar-Poli et al., 2012; Andreasen et al., 1995). The strong prevalence of body and mind control delusions, persecutory delusions and thought broadcasting are characteristic of delusion types that have been associated with schizophrenia. These specific delusions occur in greater incidence in schizophrenia, disproportionate to other psychiatric disorders such as depression or bipolar disorder (Appelbaum et al., 1999).

Nabilone did not have a significant effect on the Hallucination and Delusion Dimension. This could imply that cannabinoids do not play a significant role in the expression of this dimension and associated schizotypy components. While not statistically significant Nabilone did cause a small variation in the frequency response variation. This could mean that the lack of significant effect could be due to the aforementioned individual and dose dependent responses in conjunction with a small sample size. For example, while oral administration of 10mg THC produced overall changes in positive symptoms, negative symptoms and general psychopathology in a studied sample, only 33% of subjects actually presented with transient psychotic symptoms (Martin-Santos et al., 2012). Other studies of cannabis use place a likelihood of experiencing transient psychotic symptoms between 15% and 51% (Thomas., 1996; Green et al., 2003; D’Souza et al., 2004; Morrison et al., 2009; Atakan et al., 2013). A retrospective analysis of hospital cases showed that in cases of acute cannabis toxicity only 6.5% presented with psychosis and 3.8% with hallucinations (Schmid et al., 2020).

DEX also had no significant effect on Hallucination and Delusion Dimension scores. In the context of previous studies regarding dexamphetamine and psychosis, or positive
dimensions of schizotypy, of which this dimension is so reminiscent, this result is unexpected. While there have been some previous findings of no association between elevated striatal dopamine release and schizotypy measures (Thompson et al., 2020) most studies have found the opposite (Woodward et al., 2011; Abi-Dargham et al., 2004). One possible explanation for the lack of effect may be that the dosage of DEX used was insufficient for the production of psychosis like effects. The mean dosage of the DEX study was 32.41 mg. Previous studies of DEX have reported effects of elevated mood and arousal at 20 mg (Jacobs and Silverstone, 1986). However, it is not until dosages increase to 50-100 mg that extreme disturbances in mood could be observed and until above 100 mg that symptoms of psychosis appeared (Griffith et al., 1972). It should be noted that these individuals had previous experience with dexamphetamine and may have been sensitised. Angrist found that it took a minimum of 250 mg of dexamphetamine to induce psychosis. It is possible that a higher dose of DEX may have produced significant changes in the Hallucination and Delusion Dimension.

4.3.2 Mania-like Dimension

The second MFA Dimension was primarily composed of energy, bizarre behaviour, and euphoria components. This combination of components is strongly representative of mood states and symptoms that have been associated with amphetamine usage and mania. Therefore, that DEX caused a significant increase in this dimension score compared to placebo is expected. In amphetamine studies, the most cited effects included increased energy and euphoria. Of amphetamine-dependent individuals, 85.6% reported euphoria and 81.1% reported energy as the most frequently experienced effects and that these are effects that appear to be similarly elicited between non-dependent and dependent users (Green et al., 2020). Bizarre behaviours are not commonly self-reported by users and require observations by others. Neural studies also show correlations between amphetamine-induced dopamine
release in the ventral striatum and observations of euphoria, with euphoric responses positively correlated to the magnitude of dopamine release (Drevets et al., 2001). The significant presence of these components also aligns with the established dosage effects with previous observations of 20mg DEX producing elevated mood and arousal (Jacobs and Silverstone, 1986). While there is some evidence of these components being reported in studies of cannabis, with feelings of euphoria (Martin-Santos., 2012; Wachtel et al., 2002; McDonald et al., 2003) and feelings of tension (Crippa et al., 2009) there is also strong evidence of the opposite. In this study Nabilone did not have a significant effect on this dimension. There was also a significant presence of bizarre behaviour which in a number of studies assessing factor structures of schizophrenia and schizotypy has been associated with a disorganised dimension of schizophrenia, separate to positive and negative dimensions (Andreasan et al., 1995; Bergman et al., 2000; Liddle., 1987; Raine et al., 1994; Vollema and Hoijtink et al., 2000), although some are also clearly positive symptoms (catatonia, catatonia-related excitement, bizarre mannerisms such as hair-twisting).

4.3.3 Delusional Guilt Dimension

The Delusional Guilt Dimension contributed towards 7% of the variance in schizotypy scores. A previous factor analysis study of delusions subtypes in schizophrenia identified a discrete class of delusions titled negative affect delusions that were composed of delusions of guilt, jealousy or sin (Kimhy et al., 2005). This may indicate that delusions of guilt have a neural basis separate to other delusions. Nabilone caused a significant increase in this dimension which was observed in the same Kimhy et al. (2005) factor study where the negative affect delusion was observed to be greater among people who use cannabis. DEX exhibited no significant effect on this dimension which aligns with the observed significant increases in the Mania-like Dimension which could be considered antithetical to delusional guilt.
4.4 Anxiety

As there is substantial evidence for comorbidities of anxiety disorders and anxiety symptoms in patients with schizophrenia it was assessed alongside and within schizotypy measures (Achim et al., 2009; Seedat et al., 2007; Braga et al., 2013).

4.4.1 Nabilone had no effect on anxiety

Nabilone had no significant effect on anxiety scores overall or at any time point during the testing session. Previous research into the interaction of cannabinoids and anxiety has had mixed results with observations of anxiolytic, anxiogenic or no effects at all. Clinical studies of cannabis and THC have reported increased tension and anxiety (Crippa et al., 2009) with increases in anxiety observed over a broad range of previous cannabis use. However, anxiety is the most cited mental disorder in the use of medical cannabis with reports of increased feelings of relaxation after cannabis or THC in daily users (Hart et al., 2002; Hart et al., 2001). Zuardi et al (1982) reported acute anxiogenic responses in humans following the administration of cannabinoids. However, animal studies have shown cannabinoids to induce both anxiolytic and anxiogenic responses, dependent on dose and environment (De Fonseca et al., 1996). There has been some evidence of dose specific responses with low doses of THC producing reduced self-reports of stress relieving effects while higher doses non-specifically increased negative mood overall (Childs et al., 2017). The results of this study would indicate that there was not a significant overarching effect of CB1 receptor agonists on anxiety domains, however due to the lack of statistical power it is not possible to conclusively state that there is no effect.

4.4.2 DEX increased anxiety scores

DEX increased anxiety scores which aligns with previous evidence for anxiogenic-like effects of amphetamine type stimulants in humans (Hall et al., 1996; Williamson et al.,
1997) and dose-dependent anxiogenic effects in animal studies (Simon, 1993; Lin, 1999; McLelland, 2014). Previous observations of anxiety-like behaviours have been associated with changes in meso-limbic dopamine function (Yorgason et al., 2013), for example increases in dopamine levels and the enhancements of dopamine responses to psychostimulants. A number of studies that have found that the dopaminergic system within the VTA (Radke and Gewirtz, 2012), NAc (Lecourtier et al., 2010), amygdala (de la Mora et al., 2010; Diaz et al., 2011), mesolimbic (Trainor, 2011) and hippocampus regions of the brain could play a role in the modulation of anxiogenic effects. There have been some findings of amphetamine type stimulants failing to have an effect on anxiety indices (Lister, 1987) and even observations of amphetamine induced anxiolytic effects (Dawson et al., 1995) but the results from this study support anxiogenic effects of DEX in humans.

### 4.5 Amphetamine Like and Opposite Effects

#### 4.5.1 Nabilone on AMQ-Like and Opposite

Nabilone resulted in a significant increase in AMQ-O effects compared to placebo. Amphetamine opposite effects, or withdrawal effects, as defined in the AMQ-O include feelings of irritability or annoyance, oversensitivity and paranoia, disinterest or anxiety, stress, exhaustion, feeling withdrawn or unsociable, sluggish or drowsy and sad or depressed. These specific mood states that are classified as amphetamine opposite, have been previously observed under the influence of CB1 receptor agonists. In a study that looked at synthetic cannabinoid exposure reports, 19.1% experienced agitation and irritability and 17.5% experienced drowsiness (Forrester et al., 2012). Synthetic cannabinoids have caused acute effects of drowsiness (van Amsterdam et al., 2015) and users of THC have reported issues with transient feelings of tension, agitation, dizziness and confusion (Logan, 2007). CB1 receptors have been observed to modulate amphetamine-induced behavioural responses in
animal studies, with reduced psychostimulant-elicited hyperactivity in habituated animals (Poncelet et al., 1999; Tzavara et al., 2003) and abolished amphetamine induced impulsive choices (Wiskerke et al., 2011) and synthetic cannabinoid and CB1 receptor antagonists negatively modulate DEX behavioural and neurochemical actions (Polissidis et al., 2014), however there have also been observations of opposite effects, with synthetic cannabinoid receptor agonists prompting positive mood changes (euphoria), agitation, excitability (Castellanos et al., 2011), or no effects at all (Martin et al., 2003). How the endocannabinoid system potentially modulates amphetamine induced behaviours is largely unknown. Nabilone exhibited no significant effect on AMQ-L like scores. It is also of interest that Nabilone had no significant effect on the *Mania-like Dimension* that was closely reflective of AMQ-L effects. This could suggest that any potential psychomimetic cannabinoid effects are not connected to psychomimetic effects of amphetamine or amphetamine-like psychosis.

4.5.2 DEX significantly increased AMQ-L measures

As would be expected DEX caused a significant increase in AMQ-L effects with a greater presence of amphetamine associated mood states compared to placebo. The associated mood states included feelings of elation, euphoria, pleasure, arousal or alertness, talkative or sociable, energetic, powerful and in control, productive or creative, confident and secure, excited and optimistic, tingling and buzzing. Mania-like mood states reflect the schizotypy components identified in the *Mania-like Dimension* of which DEX caused significant increases suggesting a consistent effect.

4.6 MRCI-Q scores

The significant increases in MRCI-Q scores offer confirmation that classically associated cannabis intoxication symptoms were experienced by participants under Nabilone.
This would be expected as Nabilone is a synthetic analogue of THC and has a similar pharmacology.

4.7 Phantom Word Illusion

DEX resulted in a significant increase in mean word count of the PWI indicative of increased illusory experience compared to placebo. However, while there was a significant effect of DEX on both word count and total schizotypy there was no correlation between schizotypy and word count under DEX. There have been previous observations of a lack of correlation between illusion strength and positive and negative symptoms of schizophrenia (Gzeczkowski et al., 2018). The significant effect of DEX on the PWI may indicate a propensity to auditory hallucinations and that DEX induced a greater likelihood for changed perceptual experiences. It is also possible that illusions have a different underlying neurological mechanism to hallucinations, in which case the results of this study would implicate dopamine as a potential underlier. Nabilone had no significant effect on the PWI combined with no effect on total schizotypy, or the Hallucination and Delusion Dimension.

4.8 Potential Neural Substrates

THC effects appear to have a delayed onset in comparison to other psychomimetic drugs. This may be due to differences in bioavailability or could suggest that the effects may be downstream to its primary state of action. Cannabinoids have a wide range of bioavailability, particularly those administered orally, and can be affected by a wide range of factors. If effects are downstream this could also indicate that the psychotic effects associated with cannabis are related to the activation of other neurotransmitter systems. A number of studies have suggested that dopamine abnormalities underly the psychotic symptoms of THC (Snyder, 1976; Davis et al., 1991; Howes and Kapur, 2009). In this study Nabilone and DEX affected different underlying dimensions of schizotypy components, which would suggest
there is not a common pathway for the two drug’s psychotomimetic effects. However, evidence regarding dopamine and cannabinoid interactions are mixed. Previously, single doses of dopamine receptor antagonists have been seen to reverse the acute psychomimetic effects of THC in healthy subjects (Kleinloog et al., 2010; Liem-Moolenaar et al., 2010), although not always (D’Souza et al., 2008). It is possible that the potential sedating effects of the antipsychotics may have masked the effects. Long term dopamine receptor antagonist treatments did not protect patients with schizophrenia from THC exacerbating symptoms (D’Souza et al., 2005). One pre-clinical study of THC noted increased striatal dopamine release by 25-100%, another study saw a 3.9% increase in striatal dopamine release (Bossong et al., 2015), further studies reported no significant increase (Stokes et al., 2009; Barkus et al., 2011), and some reported decreases in cannabis users with psychosis (Slifstein, 2010). Using PET, people currently using cannabis have shown lower striatal dopamine synthesis capacity in the associative and limbic subdivisions of the striatum compared to matched nonuser control subjects (Bloomfield et al., 2013). This reduction was driven by the severity of cannabis use and meeting of clinical criteria for a substance use disorder or dependence. Further, under acute cannabis there was no relationship between transient psychotic symptoms with dopaminergic function, suggesting that there were no underlying causal mechanisms of dopamine in cannabis and psychosis (Bloomfield et al., 2013). A lot of these studies were restricted by small sample sizes, used different doses, administration and methodology. Individuals with psychosis and or a family history of psychosis demonstrate THC-induced striatal dopamine release not observed in control subjects (Kuepper et al., 2013) although cannabis users with psychosis show a decreased striatal dopamine release and in comorbid schizophrenia and substance use, people using cannabis exhibited blunting of striatal dopamine release (Thompson et al., 2013). This may suggest that there are significant
individual differences in the effect on dopamine by THC effects, complicated by differences in acute and chronic use and within individuals who are at risk of psychosis.

Brain regions that contain the cell bodies and targets of efferent dopaminergic neurons also have a dense distribution of CB1R which appear to modulate dopaminergic neurotransmission through negative feedback mechanisms, but these can work in opposite direction to each other. However, there is no evidence of presynaptic CB1R on dopamine neurons, rather they are primarily located on GABAergic, glutamatergic, cholinergic and somatostatin neurons, all of which are involved in the striatal circuitry that dopamine modulates. It is possible that cannabinoid agonists may influence dopaminergic neurotransmission largely through indirect mechanisms and GABAergic and glutamatergic systems (Fitzgerald et al., 2012). Chronic cannabis use has been associated with reduced glutamate levels (Prescot et al., 2013). Both CB1 receptors and the glutamatergic system have direct and indirect interaction in a number of brain regions that have been implicated in putative psychosis. There is also a substantial preclinical data that supports an interconnection between cannabinoid and GABA systems (Radhakrishnan et al., 2015; Eggan et al., 2010; Bartos and Elgueta, 2012; Klausberger et al., 2005; Farkas et al., 2010; Curley and Lewis, 2012; Volk and Lewis, 2015). The differential schizotypic effects combined with Nabilone exhibiting significant increases in amphetamine opposite like effects may suggest a complex interaction between the two neurotransmitter systems.

Current evidence is contradictory and insufficient to provide clarity in regard to potential underlying mechanisms or overall outcomes. Our results favour the view that CB1 agonists have schizotypy effects independent of dopamine, but also exhibit some dopamine opposite effects, especially in terms of mood. Potentially, these results could extend to allow for predictions of THC psychotic effects in individuals. For example, in individuals who exhibit high baseline Mania-like Dimension schizotypy components, THC may act as an anti-
psychotic. In turn, those individuals who express high delusional guilt may find THC to have a pro-psychotic effect. Further exploring specific underlying schizotypy components in the context of potential underlying neural substrates may allow for future predictions of different consequences for prescription and recreational drug use.

4.9 Limitations

4.9.1 Sample size and statistical limitations

There were a number of limitations in this study, the most significant of which was the limited sample size. This issue is further exacerbated by the inherently heterogeneous nature of drug response and large variance in individual response that makes it difficult to identify broader patterns within a small population. The small number of participants meant that there was limited statistical power which may not have allowed for the accurate identification of potential drug effects. The decision regarding the type of statistical test to use in the analysis of data can have a profound effect on the end results and subsequent interpretation. Parametric tests operate on assumptions of equal variance and a normal distribution of data. However, real data is not often exactly normal (Bridge and Sawilowsky, 1999; Hill and Dixon, 1982; Micceri, 1989) and in smaller sample sizes it is less likely that frequency distributions will approach normality. Human studies all violate a basic assumption of parametric statistics: random allocation to groups or treatments. While ours was a within-subject study, there is a self-selection sampling bias as all participants were volunteers, who are not typical of the population as a whole, and had some interest in experiencing psychotropic drugs. There have been conflicting arguments regarding the use of parametric or non-parametric tests, especially in regard to non-normally distributed data. Convention would dictate a standard use of non-parametric tests where there is non-normally distributed data (Altman et al., 1983). Some studies with small samples sizes and non-
normally distributed data have even demonstrated greater statistical power with the use of non-parametric tests compared to parametric tests (Weber and Sawilowsky, 2009; Tanizaki, 1997; Bridge and Sawilowsky, 1999). However, others have argued that the cost of power in the application of non-parametric test makes it too conservative (Janušonis, 2009; De Winter, 2013; Sawilowsky and Hillman, 1992; Zimmerman and Zumbo, 1992). It has even been suggested that in a small sample size it is not appropriate to assess normality and that parametric tests should be used as a default. Some researchers have started using parametric tests when the data roughly displays a normal distribution or when non-parametric tests exhibit low to zero power when not taking account the normality. Generally nonparametric tests have been shown to be inferior to parametric when parametric assumptions are met however it is difficult to judge if standard parametric tests can be suitably valid of non-normal data especially in small sample size studies. For this study parametric methods of paired t-tests were used on the AMQ-L, AMQ-O, MTB and MRCI-Q as each respective data set was found to have a normal distribution. Schizotypy data, both overall and individual MFA identified dimensions, were assessed by non-parametric tests on the basis that the data was ordinal and revealed to have skewed distributions with the suggestion that future studies could increase the sample size to increase chance of a normal distribution of data.

4.9.2 Dosage

Due to the presence of adverse effects in some individuals the dosage of Nabilone was reduced to half of the standard clinical prescription or amount that has been used in previous studies. As noted, effects of THC and cannabis have a strong dose-dependent quality. Therefore, it is possible that the lowered dosage may have meant that participants with a higher ‘tolerance’ did not show a measurable effect that may have been observable under a larger, or even standard dosage.
4.9.3 Nabilone and DEX populations

In both the Nabilone and DEX studies the majority of volunteers were drawn from a cohort of university students. However, the two samples differed in proportion of demographic characteristics, with differences in sex, age and education levels which makes joint and direct comparisons less trustworthy. Demographic factors have been observed to influence responses and drug effects so in future research using the same cohort, or a similar sample may be worthwhile.

4.9.4 Exclusion Criteria

For safety reasons there was the exclusion of any individuals who might have an obvious risk of psychosis or previous adverse experiences with cannabis. While essential from a safety standpoint it does limit the ability to generalise these results, and may have excluded the most informative individuals: those with propensity towards psychosis.

4.10 Concluding Remarks

There have been few studies that have focused on the underlying components of schizotypy at a factor-level, despite evidence of unique neural substrates. The use of global measures, or predetermined three-factor models, while potentially more efficient, may result in the loss of important data. The present study utilised drug challenges of Nabilone and DEX, using schizotypy as a model for schizophrenia, to assess possible underlying roles and interactions of cannabinoids and dopamine on specific underlying components of schizophrenia. Nabilone and DEX had different effects on overall schizotypy and underlying components, suggestive of cannabinoid agonist induced specific psychotic-like symptoms independent of dopamine. Combined with the significant effect of Nabilone on amphetamine opposite-like effects it is possible cannabinoid agonists can have a net decreasing effect on dopamine. This may have interesting implications in regard to the prediction of pro-psychotic
or anti-psychotic effects of THC in individuals. Future studies into specific components of schizophrenia may facilitate further clarification of potential neural bases of aberrance and assist in the prediction of drug effects in individuals, potentially leading to improved treatments and prevention of adverse drug responses.
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