Cortical Gyrification in Methamphetamine Associated Psychosis: A Potential Neurodevelopmental Biomarker for Risk of Psychosis

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Abstract

For many years, methamphetamine associated psychosis (MAP) has been viewed as a symptomatic, genetic, and morphological blueprint for schizophrenia spectrum disorders (SSD) (Aoki et al., 2013; Grant et al., 2012; Uhlmann et al., 2016; Yang et al., 2021). MAP is currently diagnosed as a substance induced disorder; however, many researchers suggest that MAP may represent a transition into SSD following substance use (McKetin, 2018). The current study investigated global and local gyrification indices (GI) as a potential neurodevelopmental biomarker for psychosis vulnerability in three quasi-experimental groups; methamphetamine users without psychosis (n=21), individuals with MAP (n=18) and healthy controls (n=21). Gyrification indices were determined for each participant using Freesurfer 7.2 and compared across groups with age and sex as covariates in a multivariate analysis of co-variance (MANCOVA). The results demonstrate that group membership alone significantly accounts for 32% of the variation in overall gyrification ($F(12, 106) = 1.87$, $p=.06$, $\eta^2=0.16$; *Wilk's lambda* = 0.68, $p=.04$). Follow-up ANCOVAs suggest that individuals who use methamphetamine have higher temporal gyrification than MAP and control participants, although this result was not statistically significant. There was also a significant effect of age on gyrification ($F(6, 50) = 5.37$, $p<.01$, $\eta^2=0.39$; *Wilk's lambda* = .61, $p<.01$). Further associations between gyrification and age ($r=-0.43$, $p<0.05$), cannabis use and temporal gyrification ($r=0.29$, $p<0.05$), alcohol use and temporal ($r=0.34$, $p<0.05$) and parietal gyrification were found ($r=0.26$, $p<0.05$), as well as age of methamphetamine use onset ($r=-0.40$, $p<0.05$). These results offer more evidence on the harmful effects of drug use on brain structure, posing new questions around the developmental basis of gyrification and its status as a biomarker for disease.

Keywords: methamphetamine associated psychosis, gyrification, substance use, neurodevelopmental biomarker

Introduction and Background

On a global scale, the use of methamphetamine (MA) is increasing at a rapid rate, with far-reaching implications for physical and mental health. In addition to a range of affective and cognitive deficits, MA use is a known risk factor for psychosis (Hsieh et al., 2014). The methamphetamine-associated psychosis (MAP) symptom profile closely mirrors both positive and negative symptoms found in schizophrenia and other primary psychotic disorders (McKetin et al., 2017). Approximately 30% of individuals initially diagnosed with MAP as a substance-induced psychosis receive a revised diagnosis of schizophrenia within 10 years. MAP may characterise a stress-vulnerability model for schizophrenia, whereby MA triggers a latent vulnerability to psychosis in some users (Chiang et al., 2019; Niemi-Pynttäri et al., 2013). Extensive research has highlighted a range of neural morphological and genetic similarities between enduring MAP and primary psychotic disorders, including susceptibility genes, regional homogeneity, alterations in cortical thickness, and decreased grey matter volume (Aoki et al., 2013; Grant et al., 2012; Uhlmann et al., 2016; Yang et al., 2021). When considering the literature, it is feasible that similarities of abnormal gyrification in schizophrenia and at-risk individuals may offer a novel neurodevelopmental marker for psychosis vulnerability. However, there has been no research to date investigating abnormal gyrification in individuals with MAP (Matsuda & Ohi, 2018; Palaniyappan et al., 2013).

Methamphetamine Use in the South African Context

Since 2004, methamphetamine use within South Africa has been increasing steadily, with far reaching implications for personal, interpersonal, and public health (Jones & Rayner, 2015; Meade et al., 2015; Meade et al., 2016; Plüddemann et al., 2008; Watt et al., 2014; Watt et al., 2017). From only 0.3% of drug users naming MA as their primary substance of abuse in the first half of 2002, to 42.3% by the end of the same year, MA abuse is a rapidly increasing concern (Plüddemann et al., 2008). The young age at which MA abuse begins is

also of concern, with adolescents in the Western Cape as young as 10 years reporting use in 2008 (Plüddemann et al., 2008; Weybright et al., 2016). The little research that has been conducted on the effects of this early abuse has indicated that MA can significantly reduce executive functioning in the developing brain and increase the risk of developing persistent psychotic symptoms, as well as primary psychosis disorders like schizophrenia (Cloak et al., 2011; Lecomte et al., 2013).

The Mechanism of Methamphetamine Addiction

Methamphetamines act primarily by rapidly increasing the levels of monoamine neurotransmitters, primarily dopamine within the central nervous system (CNS), with the high lipid solubility of MA allowing it to breach the blood-brain barrier with ease and speed, resulting in an almost instantaneous high (Barr et al., 2006). The structural homogeneity of the MA compound allows it to easily substitute for endogenous neurotransmitters in the nerve terminals (Ernst et al., 2000; Marshall & O'Dell, 2012). The sudden and significant increase in monoamine, particularly dopamine, levels, results in feelings of alertness, increased libido, euphoria, decreased appetite, and an overall sense of well-being that can last anywhere between 4 and 24 hours (Barr et al., 2006; Ernst et al., 2000; Hart et al., 2001; Scott et al., 2007). The psychological and behavioural effects tend to outlast other stimulants as a result of the relatively high half-life (~ ten hours) (Barr et al., 2006; Scott et al., 2007).

The rapid and excessive release of dopamine and other monoamine neurotransmitters is thought to underly the potent reinforcing properties of MA through the activation of the mesolimbic dopaminergic reward system (Barr et al., 2006; Sulzer et al., 2005; Volkow et al., 2002). Following the intense feelings of pleasure, users experience a significant depletion of dopamine and other monoaminergic neurotransmitters that results in feelings of depression, anhedonia, reductions in motivation, and fatigue, due to disruption of the motivation,

memory, and self-control circuits in the frontal cortices (Barr et al., 2006; Volkow et al., 2002). Dopaminergic projections between the nucleus accumbens (NAc), hippocampus, and amygdala and the ventral tegmental area (VTA) associated with drug-related memories, drug-seeking behaviour, and conditioned responses have been shown to be increasingly active during times of craving (Goldstein & Volkow, 2002). Higher doses of MA are required to reproduce the same intense high, and the brain requires MA to produce enough dopamine for the user to feel normal, creating a highly addictive cycle (Barr et al., 2006).

Repeated MA use can have detrimental effects on several physiological and neurological systems. Chronic use is associated with physiological effects, including hypertension, strokes, liver and renal failure, kidney disease, weight loss, and the decay and loss of teeth (Hamamoto & Rhodus, 2009; Jones & Rayner, 2015; Watt et al., 2014). Long term exposure to MA can lead to severe neuronal damage, including neuron terminal damage, inflammation, and reductions in the functionality of neurotransmitter transporters and receptors, creating the potential for persistent monoaminergic deficits (Krasnova & Cadet, 2009; Marshall & O'Dell, 2012). The processes responsible for this damage are not yet fully understood, but several potential mechanisms have been identified, including inflammation, blood-brain barrier dysfunction, dysfunction of endoplasmic reticulum and mitochondria, and oxidative stress (Barr et al., 2006; Yamamoto et al., 2010). The neuronal damage resulting from this neurotoxicity has been associated with a range of neuropsychological and behavioural deficits, that can persist even in the absence of the drug (McKetin et al., 2006; Nordahl et al., 2003).

Cognitive and Affective Deficits Following MA Use

Deficits in affective and cognitive processing following MA use are well-documented. Disruptions to the prefrontal cortex and frontal-striatal networks are associated

with deficits in executive functioning, including set-shifting, working memory, and inhibition control (Nordahl et al., 2003). Damage to inhibitory control not only results from, but also plays an active part in the addiction cycle (Garavan & Hester, 2007). Increased hostility and aggression as a result of impaired affect regulation and impulsivity seen in MA use are associated with thinner frontal cortices (Kogachi et al., 2016). Permanently disrupted emotional regulation following MA use is associated with reductions in subcortical volume in the amygdala, insula, and hippocampus, and cortical thickness reductions in the superior temporal gyrus and the anterior cingulate cortex (Kohn et al., 2014). As well as impulsivity, research has indicated that symptoms of psychosis, such as persecutory delusions, may mediate the relationship between aggression, hostility, and MA use (Lapworth et al., 2009).

Psychosis Following MA Use

Alongside the affective and cognitive symptoms seen in extended MA use, transient symptoms of psychosis can be seen following repeated administrations or sufficiently high doses (McKetin, 2017). Psychosis following MA use presents with a similar symptom profile to schizophrenia and other primary psychotic disorders. The most described symptoms include auditory and visual hallucinations, conceptual disorganization, paranoid and persecutory delusions, and depression (Voce et al., 2019). For most MA users, symptoms of psychosis do not exist outside of intoxication and withdrawal, typically subsiding within a few days or a month in the absence of the drug (McKetin et al., 2017). In some individuals, symptoms of psychosis can continue for a significantly longer period. In these cases, individuals are diagnosed with MAP as a substance-induced disorder, and sometimes a later diagnosis of a primary psychotic disorder (McKetin, 2018). There is little consensus regarding whether MAP should be defined as a substance-induced psychotic disorder, or whether it represents a latent vulnerability to primary psychosis.

Conceptual Framework

A Biopsychosocial Model and a Neurodevelopmental Approach to Psychosis

This study situates MAP within a biopsychosocial model of psychotic disorders, whereby MA use triggers acute psychosis in individuals with underlying neurodevelopmental, social, and psychological vulnerabilities (Skewes et al., 2013). A neurodevelopmental stress-vulnerability model for psychosis proposes that MAP is a unique diagnostic point within the broader collection of schizophrenia spectrum disorders (SSD), with similar symptoms, risk factors, susceptibility genes, and brain morphology (Aoki et al., 2013; Fusar-Poli et al., 2011; Grant et al., 2012; Iijima et al., 2002; Orikabe et al., 2011; Uhlmann et al., 2016; Yang et al., 2003). This neurodevelopmental approach to psychosis is supported by the later diagnostic transition to SSD in a percentage of MAP individuals (McKetin, 2018).

Problems with SSD and MAP Diagnoses

While psychosis following MA use is typically transient, some individuals can develop an enduring form of MAP (Wearne & Cornish, 2018). A difficulty exists in diagnosing individuals with MAP with symptoms that endure for longer than six months. MAP is currently diagnosed as a substance-induced psychosis, where individuals present with hallucinations or delusions that subside within a month following MA use cessation (Voce et al., 2019). This diagnosis becomes insufficient for the small minority of MAP individuals, between 10-28% who report experiencing symptoms for more than six months (Iwanami et al., 1994) or even after long periods of abstinence (Sato et al., 1992). According to the DSM-5, psychotic symptoms that persist for longer than six months warrants the diagnosis for a primary psychotic disorder (5th ed.; DSM-5; American Psychiatric Association, 2013). Differences in symptom profiles between MA users with transient psychosis, MA users with

MAP, and individuals with primary psychotic disorders may offer some insight into these diagnostic difficulties.

Symptom Profiles of MAP and Schizophrenia Spectrum Disorders

Although many researchers have failed to differentiate between primary psychotic disorders and both transient psychosis symptoms and MAP (Bramness et al., 2012), there is evidence to suggest that the types of delusions and hallucinations experienced by these individuals may help in diagnostic distinction (McKetin et al., 2017). The core positive symptoms of MAP and SSD, including complex auditory, olfactory, tactile, and visual hallucinations, delusions of reference, and thought interference, cannot be statistically differentiated between disorders. In contrast, the positive symptoms of transient psychosis following MA use only present as tactile hallucinations and persecutory delusions (McKetin et al., 2017). Furthermore, cognitive symptoms of psychosis, including executive dysfunctions, are indistinguishable between MAP and SSD individuals, but significantly different to MA users without psychosis (Arunogiri et al., 2020). The distinction between transient MA psychosis and MAP, and the similarities in symptom profile between MAP and primary psychotic disorders may reflect a clinical precipitation of primary psychosis in vulnerable individuals (McKetin et al., 2017). While the positive and cognitive symptoms of psychosis have been demonstrated to be statistically indistinguishable between MAP and SSD individuals, a diagnostic separation between the two psychotic disorders is supported by a difference in negative symptom severity and prevalence (Wearne & Cornish, 2018). Individuals with SSD typically report a higher prevalence and severity of negative symptoms, including blunted affect, emotional withdrawal, and motor retardation, when compared to individuals with acute MAP (Chen et al., 2015; Tomiyama, 1990; Wang et al., 2016).

Genetic and Morphological Similarities Between MAP and SSD

The stress-vulnerability model has a growing base of genetic and morphological support, with susceptibility genes, alterations in regional homogeneity (ReHo), grey matter volume, and cortical thickness, all showing similarities in MAP and SSD populations. Susceptibility genes related to neurogenesis, CNS neural development, and neurotransmitter systems implicated in psychotic symptoms have been identified in MAP and SSD individuals (Grant et al., 2012). Significant reductions in regional homogeneity (ReHo) in the right superior temporal gyrus that are negatively correlated with scores on the Positive and Negative Syndrome Scale (PANSS) have been documented in SSD and MAP populations (Yang et al., 2021). ReHo evaluates the level of local connectivity within a particular region by measuring the time consistency of tissue oxygenation between a single voxel and its nearest neighbours (Jiang & Zuo, 2016; Zang et al., 2004). These reductions suggest that positive and negative scores on the PANSS may be due to altered connectivity within the right superior temporal gyrus. Specific regional brain atrophies in the hippocampus, superior temporal gyrus, frontopolar cortex, and inferior frontal gyrus of the left hemisphere have been reported in MAP, SSD, and individuals with a clinical high risk (CHR) for psychosis (Aoki et al., 2013; Farnia et al., 2020; Fusar-Poli et al., 2011; Uhlmann et al., 2016).

Literature Review

The Neurodevelopmental Path to Psychosis

While the exact cause of MAP is not yet fully understood, research has highlighted a range of developmental, environmental, and genetic risk factors, many of which overlap with SSD. Perhaps the most robust predictor for enduring MAP is longer, more frequent, and more severe MA use (Arunogiri et al., 2018). Similarly, SSD individuals demonstrate earlier onset of psychosis following drug use, suggesting that drug use may trigger the onset of psychosis in the vulnerable (Marconi et al., 2016). Family history of primary psychotic disorders is

another consistent predictor of enduring MAP and SSD, highlighting a genetic risk for psychosis in both diagnoses (Chiang et al., 2019). In terms of environmental predictors, a history of sexual abuse and other adverse childhood experiences have shown to be risk factors for developing psychosis following MA use, and in the early presentation of psychosis in individuals on the SSD spectrum (Ding et al., 2014; Stilo & Murray, 2019).

Gyrification in Neurodevelopment

While abnormalities in cortical thickness within MAP populations is typically associated with the effects of MA on the brain, cortical gyrification offers a more developmentally focused alternative (Spalthoff et al., 2018). The cortical folding process that creates gyri and sulci takes place in utero and the first two years of life and is strongly influenced by genetic factors (Matsuda & Ohi, 2018). As the process of gyrification wanes after the first two years of life, with global gyrification (GI) reducing by 18% to reach the typical adult level at age 23 (Zilles et al., 1988), significant alterations in particular population (such as people with schizophrenia) offer a potential marker of neurodevelopmental disturbances (Armstrong et al., 1995). Gyrification is measured by taking a ratio of the pial surface and the smoothed outer surface within a particular region of interest (ROI), producing a local gyrification index (LGI) (Matsuda & Ohi, 2018). Abnormal gyrification denotes both increased gyrification indices, or hypergyria, and decreased gyrification indices, or hypogyria (Matsuda & Ohi, 2018).

Abnormal Cortical Gyrification in SSD

Gyrification abnormalities have consistently been confirmed in individuals with SSD and other primary psychotic disorders, as well as their familial relatives; individuals with first-episode SSD; and individuals at clinically high risk for psychosis (Matsuda & Ohi, 2018). Despite this, no studies investigating gyrification in MAP currently exist. It has long since been proposed that symptoms of psychosis may stem from disrupted connectivity in

several neural sub-networks, including the prefrontal-hippocampal network and the cerebellar-thalamic-cortical networks (Andreasen et al., 1998). As such, it may be the case that abnormal gyrification during development may result in the neural connectivity disruptions that give rise to symptoms of psychosis.

Global hypogyria has been found in individuals with chronic schizophrenia, with significant reductions in both posterior and anterior regions (Kulynych et al., 1997). Despite global hypogyria, increased LGI demonstrated in the visual cortex of individuals with schizophrenia may indicate a structural basis for deficits in visual processing associated with psychosis (Schultz et al., 2013). Furthermore, Falkai et al. (2007) found significantly increased LGI in frontal lobes of individuals with schizophrenia, as well as their asymptomatic family members, compared to healthy controls. This finding was supported by Palaniyappan et al. (2011), which demonstrated increased LGI in bilateral front marginal regions.

In terms of local hypogyria in individuals with schizophrenia, decreased LGI has been found bilaterally in ventral and dorsal regions of the prefrontal cortex (McIntosh et al., 2009; Palaniyappan et al., 2011). Follow-up studies observed the greatest decrease in LGI in the left insula, its posterior extension to the superior temporal sulcus and gyrus, and its anterior extension to Broca's area; as well as the right medial parietal region, right temporo-occipital region, and the left pericentral regions of schizophrenia patients (Palaniyappan & Liddle, 2012; Nesvåg et al., 2014). This lends additional support to the concept of LGI abnormalities acting as a potential neurodevelopmental marker for psychosis vulnerability. Overall, abnormal gyrification seems to be the defining characteristic of gyrification in chronic schizophrenia.

Abnormal Cortical Gyrification in Individuals at Risk of Psychosis

There appear to be some differences in gyrification between individuals with chronic SSD, those with first-episode schizophrenia, and individuals with a high risk for psychosis. It is possible that this may represent the progression of psychotic disorders. Recent evidence indicates widespread clusters of increased LGI in bilateral occipital regions, including the right superior parietal region, right medial orbitofrontal region, and rostral anterior cingulate gyri in first-episode schizophrenia individuals (Sasabayashi et al., 2017). This study also highlighted increased LGI in the left frontal pole. Evidence suggests that the difference between increased GI in first-episode schizophrenia and general decreased GI in chronic schizophrenia may simply be a matter of disorder progression. In a longitudinal study of adolescents with schizophrenia, Palaniyappan et al. (2013) found that at onset, these participants (aged 14.2–18.4 years) presented with decreased LGI in the right region of Wernicke's area to the posterior insula. Increased LGIs in the left fronto-insular cortex, including the anterior insula and Broca's area, at the onset of schizophrenia showed progressive decline at the two-year follow up, while LGI increased among healthy controls (Palaniyappan et al., 2013). Furthermore, increased LGI in the right prefrontal lobe was found in individuals who later developed schizophrenia, but not in familial members with similar measures of genetic liability. This may indicate that the abnormal gyrification in this area could represent a marker for transition into psychotic disorders, rather than a simple marker of vulnerability (Harris et al., 2004; Palaniyappen et al., 2013; Sasabayshi et al., 2017).

The Association Between Cortical Gyrification and Symptoms of Psychosis

Several studies have correlated the abnormal gyrification seen in schizophrenia with clinical symptoms of psychosis (Cachia et al., 2008; Kubera et al., 2018; Sallet et al., 2003; Sasabayashi et al., 2017). When compared with symptom scores on the Brief Psychiatric

Rating Scale (Overall & Gorham, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Negative Symptom Rating Scale (Iager et al., 1985), paranoid symptoms appear to be positively related to increased GI, and negative symptom severity was shown to be inversely associated with GI values (Sallet et al., 2003). Furthermore, results of an LGI study indicated that increased LGIs in the right parahippocampal gyrus, the right insula, and right temporal pole, were related to positive symptom severity (Sasabayashi et al., 2017). Persistent auditory hallucinations (a core symptom of SSD, MAP, and other primary disorders of psychosis) (Garrison et al., 2019) were related to decreased LGI in the right Broca's area, although this correlation was not statistically significant (Kubera et al., 2018). Taken together, these studies provide strong evidence for further investigating the possibility that the abnormal gyrification seen in schizophrenia and related to psychotic symptoms presence and severity are also seen in MAP.

Rationale

Despite extensive research into the symptomatology and structural markers of MAP, a concrete understanding of the relationship between methamphetamine use, enduring psychosis, and primary psychotic disorders remains unclear. The difference in symptom profiles between transient psychosis and MAP, in tandem with the overlap between both symptomatology and structural changes in schizophrenia and MAP, provide tentative support for the stress-vulnerability model. To successfully treat individuals with enduring MAP, it is necessary to have a clear understanding of the disorder and its relationship to primary psychotic disorders. Structural parallels between SSD and MAP, including measures of regional homogeneity, genetic markers, cortical thickness, and subcortical volume allow insight into the effects of methamphetamine on the brain. Cortical gyrification offers a more developmentally oriented marker for vulnerability to psychosis, with abnormalities in development seen in patients with schizophrenia and those with a high risk of psychosis.

However, there has been no research into potential gyrification abnormalities associated with MAP. Potential evidence of similar patterns of cortical gyrification in MAP and primary psychotic disorders could provide additional support for the development of MAP following MA use, highlighting a developmental vulnerability to psychosis.

Hypothesis and Aims

This study aims to explore cortical gyrification in three quasi-experimental groups, methamphetamine dependent individuals without psychosis (MA), methamphetamine dependent individuals with symptoms of psychosis (MAP), and healthy controls. Local gyrification indices (LGI) will be assessed for the whole cortex and will then be compared with scores on the positive and negative syndrome scale (PANSS) to determine whether there is a relationship between differences in cortical gyrification and symptoms of psychosis. The study hypothesises that:

1. MAP participants will demonstrate global gyrification index differences when compared to the MA and control participants.
2. MAP participants will demonstrate increased LGIs in the right prefrontal lobe, right temporal pole, the right superior parietal region, right medial orbitofrontal region, rostral anterior cingulate gyri, and the left fronto-insular cortex, including the anterior insula and Broca's area.
3. The pattern of gyrification will not differ between the MA participants and healthy controls.
4. Patterns of abnormal gyrification in MAP participants will be associated with symptoms of psychosis.

Methods

Study Design

The data for the proposed study was collected for research in 2014 (Cotton, 2014; Uhlmann, 2014). This study employed a case-control research design to address a new question -the potential relationship between MAP and abnormal gyrification. There are two primary elements to the study design. Firstly, a gyrification analysis of the previously collected MRI data was conducted using FreeSurfer software, (version 4.0.5, http://surfer.nmr.mgh.harvard.edu) and the differences between the three quasi-experimental groups was compared (MA-dependent group with no history of psychosis; MAP group; and the healthy control group). Secondly, the local gyrification index (LGI) score was compared with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) data to investigate the relationship between abnormal gyrification and psychosis symptoms within the MAP group only.

Participants

The study sample (N = 60) was divided into three quasi-experimental groups; participants with MA dependence but no history of psychosis (MA group; n = 21); MA-dependent participants with a history of MA-associated psychosis (MAP group; n = 18; and healthy controls (CTRL group; n = 21). Participants were matched across all three groups based on sex and age, and all were right-handed. Participants were recruited from communities, hospitals, and drug rehabilitation facilities in Cape Town. Participants in the MA-dependant and the MAP groups were recruited from different facilities, which is noted as a limitation for this study. Before participation, trained clinicians of the Department of Psychiatry and Mental Health at the University of Cape Town carried out a clinical assessment of all participants using the structured clinical interview (SCID) for the

Diagnostic and Statistical Manual of Mental Disorders, revised text (DSM-IV-TR) (First et al., 2002).

Exclusion criteria

Participants were excluded from the original sample based on the following factors:

- current or lifetime diagnosis of any other psychiatric disorders
- a history of neurological or medical illness, or head trauma
- seropositive for HIV
- additional substance dependencies outside of methamphetamine and nicotine (MAP and MA groups), and any substance dependencies outside of nicotine for the control group
- present with known claustrophobia or MRI contraindications
- history of psychosis prior to MA use

For the MAP group, individuals who had undergone a period of longer than 12 weeks of treatment at the time of scanning were excluded. This aimed to reduce the potential confounds of antipsychotic medication on morphological structure. Within the MAP group, all but two participants were receiving haloperidol at the time of data collection. These two participants ended their medication five and three months before participation, respectively. While several participants in all three groups used cannabis, it was determined by the original authors that this use was recreational and did not amount to a dependency (Cotton, 2014; Uhlmann, 2014).

Procedure

Following approval of the ethical application, the MRI data was analysed using the FreeSurfer MATLAB gyrification tool. Global and local gyrification indices were produced and compared across the quasi-experimental groups using MANCOVA.

Ethical Considerations

The researcher has been granted full permission from the study primary investigator to access the demographic, MRI, and PANSS data from the previous study by Cotton (2014) and Uhlmann (2014). As part of the informed consent form, provisions were given for the sharing and future use of the data (see Appendix A). In the original study, after receiving a comprehensive explanation of the study protocol, each participant provided written informed consent. Participants received local supermarket food vouchers after completing the study. Ethical clearance was provided by the Human Research Ethics Committee in the Faculty of Health Sciences at UCT (HREC/REF: 692/2013). To gain ethical clearance from the UCT's Faculty of Health Sciences to use the data for this study, the researcher applied for a new protocol which was granted.

In accordance with the Belmont principles of respect for persons, justice, and beneficence, the use of secondary neuroimaging data in this study requires transparency of research procedures and the integrity of the work (Brakewood & Poldrack, 2013). To protect the participants, reduce risk, and ensure anonymity, the data was de-identified before being released to the researcher. Furthermore, only the researcher had access to the data which was stored on a secure laptop. In terms of beneficence, the re-examination of this neuroimaging data with a different research goal will add to the body of knowledge about methamphetamine-induced psychosis and potential morphological indicators of psychosis risk. This knowledge may influence procedures to improve human health and care (Brakewood & Poldrack, 2013).

Measures

Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al., 1987) is a clinical Likert-type continuous scale that measures general psychopathology and positive and negative symptoms of psychosis. The measure was administrated by the original researchers (Uhlmann, 2014). It is widely regarded as yielding a

reliable assessment of symptoms (Emsley et al., 2003; Kay et al., 1989; Appendix B). The scale consists of 30 items, with seven measuring positive symptoms (such as delusions and grandiosity), seven measuring negative symptoms (such as blunted affect and stereotyped thinking), and 16 items measuring general symptoms of psychopathology (such as anxiety and poor impulse control). Each item is rated by the clinician on a scale from '1' (absent) to '7' (extreme). Scores for each of the three subscales are added together, with the positive and negative scores having a range of 7–49 and the general psychopathology scores having a range of 16–112 (Kay et al., 1989). Within this study, the PANSS has poor internal consistency with a Cronbach's alpha of 0.57, likely due to the small sample it was administered to (n=18).

MRI Imaging Acquisition

The MRI imaging was carried out using a Siemens Magnetom Allegra 3T system at the Cape Universities Brain Imaging Centre (CUBIC). 160 1mm thick sagittal images were produced using a T1-weighted, high-resolution 3D-MEMPRAGE sequence (scan parameters: TR=2530ms; graded TE=1.53, 3.21, 4.89, 6.57ms; flip angle=7°; FOV=256mm). At this stage, participants were screened using fluid-attenuated inversion recovery (FLAIR) transversal images (TR=4200ms; TR=95ms; flip angle=150°; FOV=230mm; slice thickness=5mm) and transversal T2-weighted images (TR=9000ms; TR=96ms; flip angle=180°; FOV=230mm; slice thickness=5mm). These scans were examined by a qualified radiologist who was blind to diagnosis, and one participant was excluded from the dataset due to poor scans and appropriately referred for follow-up.

Gyrification Analysis

As this study was a secondary analysis, the researcher was provided with raw MRI images and the basic demographic data collected in the original study. All image processing and statistical analysis presented in this thesis was completed for this secondary analysis by

the researcher. This study used FreeSurfer 7.2 (FreeSurfer (harvard.edu)) with MATLAB to determine the local gyrification index (LGI). The LGI measurement is based on the surface-based morphology (SBM) technique, which mathematically determines the smoothed surface and automatically defines the pial surface (Matsuda & Ohi, 2018). Using the FreeSurfer software, 3D models with over 300,000 vertexes were created from 2D MRI data. The ratio of the outer smoothed surface and the pial surface within a spherical region of interest (ROI) were used to produce an LGI value for each vertex. The LGI values were overlaid on the cortical surface, and correct LGI values typically fall between 1 and 5, with a minimal threshold set at 1. Once the LGI value were mapped onto each average template subject, contrasts of the vertex-wise analysis were performed using Query Design Estimate Contrast (QDEC). Finally, a surface-based group analysis was conducted with a general linear model (GLM) to assess the regional group LGI differences at each vertex for the left hemisphere.

Following the LGI analysis, quality control metrics were carried out using visual inspection and outlier detection. The Euler number was generated by the FreeSurfer software and used in the statistical models as a quantitative measure of the scan quality (Dale et al., 1999).

Data Analysis

Statistical analysis was performed with the R Studio package (version 1.2.5.033), maintaining a significance threshold of 0.05 throughout. Analysis began with descriptive statistics, with the study groups (MA, MAP, and CRTL) being compared across drug use and demographic variables, including sex, age, and period of use, using chi-square tests on categorical data and correlational analysis for continuous data.

The relationship between group membership and global GI and LGI was investigated using a multiple analysis of covariance (MANCOVA). The data was first analysed to determine whether the assumptions of MANCOVA were met before proceeding. The relevant

post-hoc procedures were carried out producing Wilk's Lambda statistics. Finally, a simple linear regression model was constructed to determine whether PANSS scores are predictive of LGI in the identified areas for the MAP group only.

Results

Descriptive Statistics

Prior to conducting the MANCOVA and the regression analysis, basic demographic data was analysed by group. The final sample consisted of 60 participants separated into three quasi-experimental groups, those with methamphetamine associated psychosis (n=18), individuals who use methamphetamine without the associated psychosis (n=21), and healthy controls (n=21). As can be seen in Table 1, participants were roughly matched for age and sex, with an average age of 25 and each group having 16 men and five or two women. All three groups were compared across biological sex, use of cannabis, alcohol, methaqualone, and nicotine, using chi-squared tests. Group differences in age and the difference in period of use of methaqualone between MA and MAP participants was analysed using Pearson correlations. The results indicated that between the three groups there was a significant difference in only nicotine use ($\chi^2=12.87$, $p<.01$) and there was a significant difference in methaqualone use ($\chi^2=7.40$, $p<.05$) which is to be expected from the control group.

Table 1

Demographic Characteristics of the Study Sample

Characteristics	MAP (*n*=18)	MA (*n*=21)	Control (*n*=21)	Full Sample (*n*=60)	**	*p*
Age at Scan						
M(SD)	24.8 (6.9)	25.9 (5.6)	24.5 (5.5)	25.1 (5.9)	-0.09	.5
Sex						
Male	16(88%)	16(76%)	16(76%)	48(80%)	1.27	.5
Cannabis						
Yes	7(38%)	5(23%)	6(28%)	18(30%)	1.08	.6
Alcohol						
Yes	6(33%)	13(61%)	6(28%)	25(41%)	5.53	.06
Methaqualone						
Yes	5(27%)	2(9%)	0(0%)	7(11%)	7.40	.02*
Nicotine						
Yes	17(94%)	16(58%)	9(42%)	42(70%)	12.87	.01*
Period of Use						
M(SD)	5.6 (3.1)	5.9 (3.8)	-	-	-0.05	.8

Note. (a) * indicates a significance of p<.05. *(b)* ** the group comparison statistic was χ^2 for sex, cannabis use, methaqualone use, alcohol use, and nicotine use, and for age and period of methamphetamine use the significance statistic is *r*.

Correlates of Gyrification

Processing of the gyrification data involved the creation of a global gyrification index (GI) and regional or local gyrification indices (LGIs) for each lobe, using the Desikan atlas

(2006) and creating an index for the frontal, parietal, temporal, occipital, and cingulate cortices. Pearson correlations were computed for the continuous variables, and one-way ANOVAs were calculated for the categorical demographic variables. Gyrification did show several significant correlations with demographic variables including age, age of methamphetamine use onset, and methamphetamine abstinence. Sex and the use of cannabis and alcohol showed several significant associations with global and local gyrification values, irrespective of group membership. These results are presented in Table 2 below. These results suggest that it is important to take age and sex into consideration as covariates for the MANCOVA and ANCOVA analyses. Furthermore, they highlight the extent to which gyrification can be impacted by both biological (age and sex) and environmental factors (substance use).

Global gyrification demonstrates strong significant negative correlations with age at scan in years ($r=-.43$, $p<.05$), the age at which participants began to use methamphetamine ($r=-0.40$, $p<0.05$) for the MA and MAP groups. Frontal gyrification ($r=-.46$, $p<.05$) and parietal gyrification ($r=-.45$, $p<.05$) were also negatively correlated with age at scan in years. Parietal gyrification was additionally significantly correlated duration of methamphetamine abstinence ($r=.38$, $p<.05$). Temporal gyrification was negatively associated with participant age at the scan ($r=-.49$, $p<.05$) and the age at which methamphetamine use began ($r=-.38$, $p<.05$). Occipital gyrification was negatively correlated with age at scan ($r=-.32$, $p<.05$), and cingulate gyrification was negatively associated with both age at scan ($r=-.49$. $p<.05$) and age of onset of methamphetamine use ($r=-.38$, $p<.05$). Global gyrification was significantly different between biological sexes ($F=5.75$, $p=.02$) ($r=-.30$, $p<.05$), with women having a lower global GI value ($M=2.4$) than men ($M=2.5$).

Table **2**

The Relationship Between LGI and Demographic Variables

	Correlation			ANOVA					
	Age at Scan (Years)	Age of Meth Use Onset (Years)	Meth Abstinence (Days)	Alcohol Use		Cannabis Use		Sex	
				F	*p*	*F*	*p*	*F*	*p*
Global	**-.43*** **	**-.40***	-.06	0.26	.61	0.53	.47	**5.75**	**.02***
Frontal	**-.46*** **	-.31	-.12	1.82	018	0.46	.50	3.21	.08
Parietal	**-.45*** **	-.29	**.38***	**4.13**	**0.4***	2.19	.15	0.42	.52
Temporal	**-.49*** **	**-.38***	.23	**7.57**	**.01****	**5.22**	**.03***	2.63	.11
Occipital	**-.32***	-.30	.13	0.004	.95	0.05	.83	1.44	.24
Cingulate	**-.49 *** **	**-.38***	.06	1.04	.31	0.81	.37	1.99	.16

Note. Pearson's correlations are presented for age at scan, age of onset, and abstinence. One-way ANOVAs are presented for alcohol and cannabis use and sex. * Indicates p<.05, ** indicates p<.01.

Cannabis Use and Temporal Gyrification

A one-way Anova indicated that temporal gyrification differed significantly on the basis of cannabis use (F=5.22, p=.03), with users having significantly higher temporal LGI (M=4.61) than non-users (M=4.41). A pairs panels analysis determined that cannabis use was positively correlated with the total temporal lobe gyrification (r=.29, p<.05). More specifically, cannabis use was associated with differences in the middle temporal gyrus (r=.26, p<.05), the superior temporal gyrus (r=.29, p<.05), and the temporal pole (r=.30, p<.05). The general trend, shown in the table below, is that the GI values for each area are typically higher for cannabis users than non-users. An independent sample t-test indicated that the difference in overall temporal GI between cannabis users and non-users was significant (t=-2.07, df=26.37, p<-.05), with the mean temporal lobe GI for the user group (M=4.6) being higher than that of the non-users (M=4.4). These results are presented in table 3.

A simple linear regression using cannabis use as a single predictor for the overall temporal GI produced a weak but significant model to predict only 7% of the variation in temporal GI in this sample population by cannabis use ($R2$=0.08, F (1, 58) =5.22, p<.05). A post-hoc power analysis determined that this model had a low level of power (.58), indicating that it only has 58% chance of detecting a statistically significant result when there is one. A larger sample size is required in order to reach a more statistically sound conclusion about the relationship between cannabis use and temporal gyrification.

Table 3

Comparing Mean Temporal LGI values for Cannabis Users and Non-Users by Group

	Cannabis Users			Non-Users		
	Control (n=6)	MA (n=5)	MAP (n=7)	Control (n=15)	MA (n=16)	MAP (n=11)
Superior Temporal	4.72(0.45)	4.65(0.30)	4.49(0.36)	4.26(0.28)	4.57(0.23)	4.38(0.29)
Middle Temporal	3.79(0.13)	3.67(0.08)	3.67(0.21)	3.51(0.12)	3.67(0.14)	3.57(0.15)
Temporal Pole	2.74(0.15)	2.69(0.10)	2.57(0.17)	2.54(0.17)	2.54(0.17)	2.60(0.14)
Temporal gi	4.73(0.45)	4.65(0.30)	4.49(0.36)	4.26(0.28)	4.57(0.23)	4.37(0.30)

Note. Mean and standard deviation values are presented above.

Temporal GI was additionally associated with age at the scan ($r=-.49$, $p<.01$) and the age that methamphetamine use began ($r=-.38$, $p<.05$). A second linear regression model including these two additional variables explained more of the variance in temporal gyrification, but the variables themselves were not significantly predictive ($R2=0.20$, F (3, 35) $=2.91$, $p<.05$). A post-hoc power analysis was performed as the subgroup for this analysis was very small (n=18). Again, a moderately lower power level of .56 was observed for this model, suggesting a 44% chance of making a type II error and missing significant results.

Table 4

Regression Results for Temporal Gyrification Using Scales as Criterion

		b		*Beta*		*sr2*		
Predictor	*b*	95% Cl [LL, UL]	*beta*	95% Cl [LL, UL]	*sr2*	95% Cl [LL, UL]	*r*	Fit
(Intercept)	4.48**	[4.40, 4.56]						
Cannabis	0.21*	[0.03, 0.38]	0.29	[0.04, 0.54]	.08	[.00, .23]	.29*	
								R2=.08*
								95% Cl[.00, .23
(Intercept)	5.03**	[4.65, 5.40]						
Cannabis	0.06	[-0.14, 0.25]	0.09	[-0.22, 0.41]	.01	[-.04, .06]	.11	
Age	-0.02	[-0.04, 0.01]	-0.41	[-0.95, 0.14]	.05	[-.07, .18]	-.44**	
Onset	-0.00	[-0.03, 0.03]	-0.03	[-0.58, 0.52]	.00	[-.01, .01]	-.38*	
								R2=.20*
								95% Cl[.00,.37]

Note. A significant *b*-weight indicates the beta-weight and semi-partial correlation are also significant. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *sr^2* represents the semi-partial correlation squared. *r* represents the zero-order correlation. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * Indicates $p<.05$, ** indicates $p<.01$.

Alcohol Use and Temporal and Parietal Gyrification

Furthermore, parietal LGI was significantly different on the basis of alcohol consumption, with those who use alcohol having higher parietal LGI (M=3.84) than those who do not (M=3.74). Temporal gyrification also differed significantly on the basis of alcohol (F=7.57, p<.01). Alcohol use was associated with higher temporal LGI (M=4.60) than non-use (M=4.38). A pairs panels analysis showed that this difference lay in particular in the superior temporal gyrus (r=0.34, p<.05) and the postcentral gyrus (r=0.26, p<0.05).

Gyrification Across the Quasi-Experimental Groups

An initial MANOVA analysis was conducted to determine whether there is any significant difference in both global and local gyrification between the three study groups. The results of the MANOVA indicate that gyrification is significantly different between the three quasi-experimental groups, with 32% of the variance in gyrification being significantly explained by group (F(12, 106) = 1.87, p=.06, η^2=.16; *Wilk's lambda* = .68, p=.04). This difference is most prominent in the temporal lobe, with the MA group (4.59) having a higher LGI than the MAP (4.42) and control (4.40) groups. There is also a group difference in global gyrification, with the MA group (2.49) once again having a slightly higher GI than the MAP (2.45) and control (2.46) groups. The partial eta squared value (η^2=.16) indicates a large effect size for this model, despite the low power of .17, suggesting that the differences seen in gyrification between groups must be strong to be picked up. This result suggests that with a larger sample with increased power, gyrification may demonstrate significantly large differences between individuals with MAP, methamphetamine use, and healthy controls.

A secondary multiple analysis of covariance (MANCOVA) was conducted with age and sex as covariates as age was significantly negatively correlated with global and all local GIs while sex demonstrated a negative correlation with global GI. The addition of the

covariates demonstrated a significant difference in gyrification based on age ($F(6, 50) = 5.37$, $p < .01$, $\eta^2 = .39$; *Wilk's lambda* = .61, $p < .01$). Despite no overall effect of sex on gyrification in this MANCOVA, a closer inspection of the results demonstrate a significant effect of sex on global gyrification ($F(1,55) = 4.99$, $p < .05$), mirroring the correlation seen initially. Difference in gyrification based on group membership was close to significance ($F(12, 102) = 1.80$, $p = .06$, $\eta^2 = .17$, *Wilk's lambda* = .66, $p < .05$). A post-hoc power test demonstrated that the sample size does not provide sufficient power to reliably interpret these results (power=0.17), although the effect size demonstrated by partial eta squared ($\eta^2 = .17$) was large. The reduced power indicates that the models had an 83% chance of missing results, leading to the conclusion that the lack of significant effects in this sample does not mean there are none, and the significant results seen are strong. These significant findings may become more significant with an increased sample size, and the findings that boarder significance may become significant.

Table 5

Results of MANOVA and MANCOVA Using Gyrification to Differentiate Groups with Age and Sex as Covariates

	df	*approx.* F	Wilks	*p*	η^2
MANOVA					
Group	2	1.87	.68	.046*	.16
MANCOVA					
Group	2	1.95	.66	.04*	.17
Age	1	5.37	.61	>.01*	.39
Sex	1	1.11	.88	.37	.12

Note. (a) * indicates statistical significance. *(b)* η^2 reports the partial eta squared value.

The mean values for each LGI grouping and the GI value by group are presented in the table below. The covariates for the MANCOVA are presented in the same table alongside the results of one-way ANCOVAs used to determine whether global and local GI differ between groups. The MANCOVA covariate results clearly demonstrate that age has a statistically significant association with global and all local gyrification indices. The results of the one-way ANCOVAs demonstrate no significant differences in global GI or LGI between the three groups, however, the difference in temporal gyrification between groups was close to statistical significance ($F(1, 56)= 3.77$, $p =.06$), with the MA group having a higher mean LGI (M=4.6, SD=0.2) than the MAP (M=4.4, SD=0.3) and control (M=4.4, SD=0.4) groups. This pattern is replicated in the MANCOVA analysis, where group was close to significant and showed the greatest effect for temporal GI ($F(2,55)= 2.96$, p=.06). It is possible that with a larger sample and more statistical power, this difference would become significant.

Table 6

Gyrification Indices by Group Compared by One-Way ANCOVA and MANCOVA

	MAP	MA	Control	ANCOVA		MANCOVA					
						Group		Age		Sex	
GI	*M*(SD)	*M*(SD)	*M*(SD)	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Global	2.45(0.13)	2.49(0.11)	2.46(0.13)	0.78	.38	0.88	.42	15.33	>.01**	4.99	.03*
Frontal	2.14 (0.10)	2.16 (0.11)	2.16 (0.12)	0.00	.99	0.30	.74	16.23	>0.1**	2.33	.13
Parietal	3.76 (0.21)	3.81 (0.65)	3.77 (0.23)	0.50	.48	0.48	.62	15.37	>.01**	0.05	.82
Temporal	4.42 (0.32)	4.59 (0.24)	4.40 (0.39)	3.77	.06	2.96	.06	23.12	>.01**	1.93	.17
Occipital	3.18 (0.21)	3.14 (0.21)	3.15 (0.24)	0.02	.88	0.20	.82	6.38	.01*	0.61	.44
Cingulate	2.03 (0.13)	1.99 (0.09)	2.04 (0.12)	2.01	.16	1.60	.21	16.78	>.01**	0.79	.38

Note. * Indicates $p<0.05$, ** indicates $p<0.01$.

The Relationship between PANSS Score and Global Gyrification

A pairs panel analysis indicated that there was no significant or strong correlation between the PANSS total score or the scores of the positive and negative subscales with the global GI or any of the local GI values. Total PANSS score was minimally negatively correlated with parietal LGI (-.28), temporal GI (-.37), and occipital GI (-.36). The negative PANSS subscale was minimally associated with frontal GI (.25) and temporal GI (-.30). Regardless, a linear regression analysis was carried out to determine whether PANSS total score was predictive of global GI. Only the total PANSS score, and global GI were used in this model as adding the positive and negative subscale scores and the LGI values would have resulted in high multicollinearity. The results of the linear regression demonstrate that a total PANSS score is unable to accurately predict global GI in this sample population (R^2=-0.00, $F(1, 16) = 0.00$, p=.96). The adjusted R^2 value of -0.06 indicates that scores on the psychosis measure can only accurately account for 6% of the variation in global GI within this sample, but there is no statistical significance to this result. A post-hoc power analysis with an effect level of .15 indicated that this model had insufficient power (power=.34), likely due to the small sample (n=18). As such, a potential relationship between symptoms of psychosis and gyrification indices cannot be ruled out in this study.

Table 7

Regression Results for PANSS and Gyrification Using Scales as Criterion

			b		*Beta*		sr^2		
Predictor	*b*	*p*	95% Cl [LL, UL]	*beta*	95% Cl [LL, UL]	sr^2	95% Cl [LL, UL]	*R*	Fit
(Intercept)	2.46**	.001	[2.29, 2.62]						
PANSS	-0.00	.96	[-0.00, 0.00]	-0.01	[-0.54, 0.52]	.00	[.00, .04]	-.01	
Total									R^2=.00
									95% Cl[.00,.04]

Note. A significant *b*-weight indicates the beta-weight and semi-partial correlation are also significant. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. sr^2 represents the semi-partial correlation squared. *r* represents the zero-order correlation. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * Indicates $p<.05$, ** indicates $p<.01$.

Predicting Global Gyrification

A hierarchical linear regression was created to explore how these variables perform as predictors for global gyrification in this experimental sample. In the first step, age at the time of scanning was included as the only predictor value, given its strong negative association with global gyrification and local gyrification indices. The results of this model suggest that age (t=-0.62, $p < .05$) can significantly but minimally predict (adjusted R^2=0.17) a lower global gyrification index ($R^2 = 0.18$, F (1, 58) = 13.13, p<.05). In the second step, the age at which methamphetamine use began was entered as a second predictor variable. The predictive strength of this model was lower than the first model. Age was no longer significantly predictive of global gyrification (t =-0.44, p =.67) and the age at which methamphetamine use began did not add any predictive power to the model (t =-1.13, p =.27). The percentage of variance in global gyrification reduced from 17% to 12%, although the model was still significant (R^2 =0.12, F (2, 36) = 3.51, p<.05).

Table 8

Regression Results for Global Gyrification Using Scales as the Criterion

		b		*Beta*		*sr²*		
Predictor	*b*	95% Cl [LL, UL]	*beta*	95% Cl [LL, UL]	*sr²*	95% Cl [LL, UL]	*R*	Fit
(Intercept)	2.69**	[2.57, 2.82]						
Age	-0.01**	[-0.01, -0.00]	-0.43	[-0.67, -0.19]	.18	[.04, .35]	-.43**	
								R^2=.19*
								95% Cl [.04,.35]
(Intercept)	2.65**	[2.49, 2.81]						
Age	-0.00	[-0.01, 0.01]	-0.12	[-0.66, 0.43]	.00	[-.03, .04]	-.37*	
Onset	-0.01	[-0.02, 0.00]	-0.30	[-0.85, 0.24]	.03	[-.07, .13]	-.40*	
								R^2=.16*
								95% Cl [.00,.35]

Note. A significant *b*-weight indicates the beta-weight and semi-partial correlation are also significant. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *sr²* represents the semi-partial correlation squared. *r* represents the zero-order correlation. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. * Indicates $p<.05$, ** indicates $p<.01$.

Discussion

This study explored the potential relationship between local and global gyrification, and methamphetamine associated psychosis in a small sample (n=60) of South African participants. While the association between abnormal patterns of gyrification and psychotic disorders, as well as the symptomatic overlap between psychotic disorders and methamphetamine associated psychosis are well-documented, the results of this study do not support a neurodevelopmental model for psychosis vulnerability based on gyrification pattern. Gyrification indices were able to differentiate participants accurately but minimally from the three quasi-experimental study groups in a multiple analysis of covariance (MANCOVA), however, follow-up one-way ANCOVAs suggested that this difference lay in a higher temporal LGI for the MA group when compared to the MAP and control groups. Additionally, there was no significant relationship between gyrification and the total, positive, and negative scores on the PANSS scale for individuals in the MAP group. These results appear to suggest that gyrification patterns do not play a role in prolonged psychosis following use of methamphetamine. The results offer new insight into the relationship between the harmful effects of substances like alcohol, cannabis, and methamphetamine and gyrification, highlighting new questions around the developmental basis of gyrification and its status as a biomarker for disease. It is, however, important to note that the small sample size has lent very little power to the statistical results, so these conclusions need to be interpreted with caution.

The Debate Around MAP

This study aimed to shed more light on the potential relationship between methamphetamine use, MAP, and primary psychotic disorders, by determining whether individuals with MAP had markedly different patterns of gyrification than MA users without psychosis and healthy controls. Abnormal gyrification has been well-documented in SSD and

other primary psychotic disorder populations, appearing to be a neurodevelopmental biomarker for psychosis risk (Matsuda & Phi, 2018). The presence of these gyrification patterns in familial members of individuals with SSD suggests that the relationship between gyrification and psychosis is not a simple case of causation, but that disruption in these specific areas increases psychosis risk (Falkai et al., 2007). Many individuals with SSD begin to experience onset of symptoms following events that dramatically alter their brain chemistry, including trauma or drug use (Khokhar et al., 2017; de Oliveira Trovao et al., 2022). While this study did find a significant group difference in gyrification, it was MA users without psychosis who appear to diverge from controls and those with psychosis. Furthermore, the lack of statistical power afforded to this study by the small sample size requires a more cautious interpretation of these results.

The results of prior research suggest a fairly stable pattern of gyrification abnormalities associated with psychosis risk in SSD disorders, and these patterns were not found in the current study sample. While previous research suggests that individuals with chronic schizophrenia demonstrate global hypogyria (Kulynych et al., 1997), there was no significant difference in global GI between MAP individuals, methamphetamine users, or healthy controls. The patterns of local hypergyria in the visual cortex and frontal lobes (Falkai et al., 2007; Schultz et al., 2013) and local hypogyria in the ventral and dorsal prefrontal cortex, left insula, temporal gyrus, Broca's area, right medial parietal cortex, right temporo-occipital region, and left pericentral regions (McIntosh et al., 2009; Palaniyappan et al., 2011; Palaniyappan & Liddle, 2012; Nesvåg et al., 2014) found in SSD individuals were not found in the MAP sample in the current study.

While the initial aim of this study was to determine whether there were any significant differences in gyrification seen in MAP participants compared to control and MA individuals, the results of the MANCOVA and follow-up one-way ANCOVAs suggest that the MA group

differs from the MAP and control groups. Despite the small sample size, an initial MANCOVA with group as a dependent variable indicated a statistically significant but fairly small effect size of 32% of group membership on global gyrification. A series of one-way ANCOVAs demonstrated no significant differences between groups on global or any local GI, however, there was a difference in temporal gyrification, with the MA group demonstrating a higher LGI (*M*=4.59) than the MAP group (*M*=4.42) and the healthy controls (*M*=4.40). It is feasible that a larger sample size may have provided more statistically significance to this finding, and this trend should be considered for investigation in future research. The current results indicate that the MA group consistently has higher LGI in the frontal, parietal, and temporal regions when compared to the control and MAP groups. SSD research findings suggest that auditory verbal hallucinations were associated with decreased temporal LGI, particularly within the left insula and Broca's area (Matsuda & Ohi, 2018), and subtle neurological sensory and motor deficits found in SSD are also related to changes in parietal gyrification. The current results echo these findings to a certain extent, however, the lack of significant differences in LGI between the MAP and control groups requires further examination.

It is worth noting that although these results do not support the theory that MAP represents a transition into SSD, the temporal region of the brain has been previously associated with the craving cycle of active drug use and the severity of auditory hallucinations (Matsuda & Ohi, 2018; Volkow et al., 2015). Although not large or significant, the MA group used methamphetamine for a slightly longer period (*M*=5.93 years) than the MAP group (*M*=5.58). It is possible that the difference in gyrification seen between the MA and MAP groups represent a graduation of damage to this area following prolonged methamphetamine use. This is can only be suspected however, as the current study did not include an SSD group for comparison. These results provide support for the theory that MAP

may not represent a triggering of an underlying SSD risk, but rather a psychosis resulting from the detrimental effects of the substance on the brain. Future research in this area could provide a more concrete understanding of the relationship between methamphetamine use and MAP.

The Relationship Between Gyrification and Symptoms of Psychosis

While this study is the first to examine the relationship between gyrification and MAP, there is a growing body of evidence indicating that symptoms of psychosis in schizophrenia are associated with abnormal gyrification in specific regions (Schultz et al., 2013). The results of the current study, however, did not find any significant association between the positive, negative, and total symptoms of psychosis as measured by the PANSS and local or global GI for the MAP group only. There were, however, some interesting trends that considered in the light of the associations between gyrification and psychosis symptoms in SSD warrant future investigation. Temporal (r=-.37) and occipital (r=-.36) LGI values were minimally negatively correlated with the total PANSS score. Positive symptoms of psychosis in SSD populations have been previously positively correlated with increased global GI, and specifically increased LGIs in the right insula, right temporal pole, and right parahippocampal gyrus (Sallet et al., 2003; Sasabayashi et al., 2017). In the current study, there was no evidence of any relationship between the positive symptoms of psychosis and global GI or LGI values. Temporal (r=-.30) and frontal (r=.25) LGI values, specifically the temporal pole (r=-.30) was minimally negatively correlated with the PANSS negative subscale. On first inspection, these results suggest that MAP may not be linked to gyrification in the same way as seen in SSD, however, the sample size and statistical power need to be considered. As these analyses used the MAP participants only, the small sample size (n=18) resulted in little statistical power. A larger sample may provide more significant data concerning these associations between symptoms of psychosis and gyrification patterns in

MAP. The question as to whether the prolonged symptoms of MAP represent a latent vulnerability to SSD, or the result of substance induced damage to the brain remains unanswered by these results.

Psychosis as the result of Drug Use

Although this study lacked power, the differences in gyrification between the MA and MAP groups suggest that abnormal patterns of gyrification may not be responsible for the prolonged psychosis seen in the MAP group. The interaction between psychosis and substance use has been widely researched for many years, providing a growing body of evidence that individuals who use substances tend to have higher levels of psychosis, transient or enduring, than the general population (Degenhardt & Hall, 2011). Research has indicated that a range of substances including amphetamines (Tenn et al., 2003), scopolamine (Barak & Weiner, 2007), Ketamine (Chatterjee et al., 2011), PCP (Castane et al., 2015), LSD (Martin et al., 2014), cannabis (Ghosh et al., 2022), methamphetamine (Yang et al., 2020), and psilocybin (Vallersnes et al., 2016) are associated with a higher incidence of psychosis. A recent study by Ghosh and colleagues (2022) found that individuals with cannabis-induced psychosis (CIP) had lower cortical thickness, depth, and gyrification in prefrontal, parietal, and temporal regions than healthy controls. The question remains, as it does within the MAP debate, whether cannabis use alters brain morphology causing psychosis, or whether the cannabis triggers an underlying morphological predisposition to SSD (Schmitt & Falkai, 2013). Ghosh and colleagues (2022) were able to differentiate between CIP and SSD based on significant differences in cortical thickness and gyrification, but further studies are required. In the current study, there was a minimally negative association between the positive symptoms of psychosis and cannabis (r=-.26) and alcohol use (r=-.34), but these results were not statistically significant. Additionally, there was no association between

methaqualone use and psychosis, however, given the small sample size of the MAP group (n=18), it is not possible to make any definitive conclusions.

Psychosis as a Result of Damaged Neurotransmitter Systems

Given the fact that psychosis is a core symptom of methamphetamine intoxication, these results question whether the prolonged psychosis seen in MAP may result from permanent disruption to neurotransmitter systems. Individuals with MAP typically use the substance more frequently, have an earlier age of onset, and require higher concentrations of the substance (McKetin et al., 2013). The symptoms of psychosis that occur during active intoxication involve a dysregulation of cortical signalling resulting from impaired GABAergic functioning (Hsieh et al., 2014). With chronic methamphetamine use, it is thought that psychosis symptoms are related to an increase in dopaminergic signalling, and that the prolonged symptoms seen in MAP may result from permanent up-regulation following damage to these neurons (Jaehne et al., 2017). These theories have not, however, been empirically examined in humans. Damage to GABAergic and dopaminergic hippocampal systems are also known to underly symptoms of psychosis in SSD, confirming that MAP remains a good model for schizophrenia (Bansal & Chatterjee, 2021; McKetin et al., 2013). The association between decreased temporal gyrification and total and negative psychosis symptoms in this study may reflect damage to the hippocampal dopaminergic system known to be dysregulated in SSD (Grace & Gomes, 2019). While the low-powered results of this study diverge from the hypothesis that gyrification may represent a neurodevelopmental biomarker for psychosis risk, it does raise more questions about the relationship between MAP and SSD, demonstrating that further research into the mechanisms of psychosis with and without substance use is required.

Correlates of Gyrification

The results of this study suggest that gyrification may not be a reliable neurodevelopmental biomarker for psychosis risk. Despite the cortical folding process that creates the gyri and sulci taking place primarily in utero and the first two years of life (Armstrong et al., 1995; Matsuda & Ohi, 2018), previous research has indicated that several environmental factors are associated with alterations in gyrification patterns. Lack of proper nutrition as seen in Anorexia Nervosa (Collantoni et al., 2021) is another key consideration within the South African context, particularly during the first two years due to widespread poverty and lack of access to necessary resources. Use of a range of substances including methamphetamine (Hu et al., 2022), alcohol (Hua et al., 2020), cannabis (Filbey et al., 2015; Shollenbarger et al., 2015), and cocaine (Trevisan et al., 2022) all appear to be associated with abnormal cortical folding patterns. Additionally, a large body of evidence supports the general decrease in gyrification with age (Hogstrom et al., 2012; Lamballais et al., 2020; Madan, 2020). Although the current study did not find any association between gyrification and methamphetamine use or MAP, there do appear to be some negative associations between gyrification patterns and age at which methamphetamine use began, age at the time of scanning, alcohol use, and cannabis use. The results of this study raise questions about the neurodevelopmental basis of gyrification formation and the potential harm of drug-taking behaviour on brain structure and function.

Gyrification and Age

Age at the time of scanning was significantly correlated with a decrease in global GI and each local lobe GI. These results align with general trend in data suggesting that gyrification gradually decreases with age, tending to noticeably begin after the age of 18 (Cronin et al., 2017; Hogstrom et al., 2012; Madan, 2020; Yang & Tang, 2000). Synaptic pruning appears to be responsible for a gradual decrease in cortical complexity through

adolescence (Yang & Tang, 2000). Prior research also suggests that the decrease in gyrification is global, and it is associated with the decline in cognition seen with age (Lamballais et al., 2020). Age-related decreases in gyrification tend to be most prominent in areas of the default mode network, including the medial prefrontal cortex in the right hemisphere and the posterior cingulate cortex of both hemispheres (Jockwitz et al., 2017). The current study is in line with these results, as gyrification showed the greatest decrease in the cingulate cortex in association with age, although the difference was minimal. The occipital lobe showed the smallest decrease in gyrification associated with age in this sample, however, this may simply be a characteristic of this small sample population as this relationship has not been confirmed by other studies. These results add to the body of literature documenting a general decrease in gyrification with age (Lamballais et al., 2020), suggesting that gyrification may be a marker for age-related brain decline. Ultimately, the relationship between age and gyrification in the current study indicates that age needs to be considered as a covariate when evaluating substance-associated changes in gyrification.

Gyrification and Biological Sex

The topic of sex differences in gyrification and related measures of cortical thinning is another commonly studied but inconclusive one. Greater cortical complexity in females has been demonstrated (Luders et al., 2004), thought to represent greater folding necessary to fit the same sized brain in a smaller skull. Additionally, an increased rate of cortical thinning in females during adolescence in the right temporal regions is thought to be associated with faster maturation and refining of brain areas associated with social reasoning (Mutlu et al., 2013; White et al., 2010). Despite these findings, postmortem studies have demonstrated no significant differences in global or local gyrification in either hemisphere between males or females (Zilles et al., 1988). The results of this study add to the debate, with females demonstrating significantly lower global gyrification than males. It is important, however, to

note the uneven distribution of males (n=48) and females (n=12) in the current study, which impacts the reliability of these results. Future studies should aim to have an even sample of males and females to increase the confidence with which results can be interpreted.

Gyrification and Alcohol

The detrimental effects of alcohol on the brain have been well documented, and the results of this study indicate that alcohol use has a negative impact on gyrification in the parietal and temporal lobes. Significantly increased gyrification was found in these lobes, which contradicts previous research indicating that alcohol use is associated with decreased gyrification in the right orbitofrontal, temporal pole, and the left lateral occipital gyrus (Hua et al., 2020). As the pattern of gyrification is asymmetrical between the left and right hemispheres and the current study explored the left hemisphere only, this may explain why the results diverge from previous research (Kinney & Volpe (2018). Additionally, much of the research into the relationship between alcohol use and abnormal gyrification is focused on the detrimental effects of prenatal alcohol exposure as the cortical folding process is taking place (Hendrickson et al., 2017; Infante et al., 2015; Kühn et al., 2016). Infante and colleagues (2015) proposed that prenatal alcohol exposure may disrupt the normal process of neuronal migration and differentiation that drives gyrification formation in the womb, resulting in a smoother cortex with lower gyrification. Others theorize that alcohol may disrupt the formation of neuronal connections, resulting in the same cortical folding pattern (Hendrickson et al., 2017). There is a significant lack of research into the effects of alcohol consumption on gyrification in the fully developed adult brain, which may account for the divergence of the current results and prior research. It is, however, important to note that pre-natal alcohol exposure was not an exclusion criterion for the current sample. Pre-natal alcohol exposure is a significant issue in South Africa, with alcohol consumption during pregnancy rates ranging from 2.5% to 45% (Culley et al., 2013). As a result, it is important to be

cautious in these conclusions. Further studies on otherwise healthy adults are required to determine the extent to which alcohol impacts gyrification outside of disrupted neurodevelopment.

Gyrification and Cannabis

The results of this study indicated a significant association between cannabis use and increased gyrification in the temporal lobe. These findings are in line with prior research implicating the temporal lobe in substance use and primary psychotic disorders (Cadet et al., 2014). While cannabis is known to affect cortical gyrification, previous research indicates a reduction in gyrification in the prefrontal, parietal, and temporal regions, as well as lower cortical thickness in these regions (Cadet et al., 2014; Filbey et al., 2015; Ghosh et al., 2022; Mata et al., 2010; Shollenbarger et al., 2015). Mata and colleagues (2010) discovered decreased gyrification in the right frontal lobe in young adults with an average age of 25.7 years) with no other concurrent drug use. As with alcohol, the asymmetry of each hemisphere may account for the divergence of the current results, but the concurrent use of alcohol and methamphetamine in this sample may also affect the patterns of gyrification seen. Cannabis use was significantly associated with concurrent alcohol, nicotine, and methaqualone use in this sample. As such, it is difficult to differentiate between the impact of these substances on gyrification. Further research into cannabis in isolation is required to understand the extent to which it may alter cortical folding patterns in young adults. It is likely that the small sample size in the current study, in addition to cannabis use not being the centre of interest may explain the disconnect between these results and prior research.

Onset Age of Substance Use

Of particular interest and importance when discussing the potentially harmful effects of substance use in the brain is the age of onset. While methamphetamine use did not show any significant associations with gyrification in this sample, the age of onset of drug use was

significantly correlated with reductions in global GI and local GI within the temporal and cingulate cortices. Early damage to the cingulate cortex may result in a myriad of impairments in later life, most prominently in reward processing and performance monitoring, which may support ongoing substance abuse (Shenhav et al., 2013). The early impact of substances on gyrification can be seen in the significantly lower cortical gyrification in individuals with prenatal alcohol exposure compared to healthy controls, particularly in the orbitofrontal cortex (Hendrickson et al., 2017; Infante et al., 2015; Kuhn et al., 2016). The use of cannabis in adolescence and early adulthood is also associated with decreased gyrification throughout the cerebral cortex (Shollenbarger et al., 2015). The impact of drug use in adolescence and early adulthood cannot be understated, disrupting the extensive developmental changes in volume, thickness and gyrification during this period of life (Cao et al., 2017; White et al., 2011).

Limitations and Future Directions

This study faced several limitations that affect the way in which the results can be interpreted. Firstly, there are several limitations surrounding the participant sample. Sample size for this study was small (n=60) with each experimental group having between 18 and 21 participants, resulting in very little statistical power (power=.17) for the MANCOVA and fundamental covariate adjustments of age and sex. In addition, the sample was uneven in terms of male and female representation, reducing the confidence with which sex differences in gyrification could be measured. There are several barriers to recruiting participants who use methamphetamines, including legal, economic, and social concerns which may prevent participants from coming forward or influence the way in which they self-report drug use. In addition, the use of methamphetamine in Cape Town South Africa is entangled with socio-economic structures that make it difficult for potential participants to access the health and drug rehabilitation facilities from which this sample was recruited (Pasche & Myers, 2012).

This may also have resulted in a recruitment bias, where the sample is only representative of individuals who were psychologically, socially, or economically capable and willing to seek medical treatment for their drug use and psychological symptoms. Participants in the MA and MAP groups were recruited from different facilities in Cape Town, which is a noted limitation as there may be geographically tied social and economic differences between these populations, which inhibits comparability and generalizability of these results. Future research would benefit from a larger sample recruited from more diverse populations throughout South Africa.

A second limitation was the lack of data pertaining to the length of time individuals in the MAP group had experienced symptoms of psychosis for. As MAP is currently diagnosed as a substance-induced psychosis, individuals with a diagnosis experience symptoms that subside within a month of MA cessation (Voce et al., 2019). Due to the cessation after a month, it is possible that for these individuals, the effects of methamphetamine may simply linger in their system for a longer time. Currently, individuals who experience MAP for longer than 6 months are re-diagnosed with a primary psychotic disorder (DSM-5), and this is the population in which it is likely that methamphetamine use triggers an underlying predisposition to primary psychosis. The purpose of this study was to examine gyrification in individuals who are likely to be re-diagnosed later, however, as the data was originally collected with a different hypothesis in mind, there is no indication as to how long the MAP participants have experienced symptoms of psychosis. Future research should aim to sample MAP individuals who have experienced psychosis for more than 6 months, in order to further differentiate between transient methamphetamine induced psychosis and the more enduring form.

Given the significant but unexpected association between cannabis use and increased temporal gyrification, the study could have benefited from more data surrounding cannabis

use, including age of onset and frequency of use. Additionally, as cannabis was not the focus of the study, only 30% of the participants reported that they use cannabis, resulting in an even smaller sample and very limited statistical power. The results of this study indicated that age of methamphetamine onset was significantly negatively associated with global, temporal, and cingulate gyrification, indicating that the damage to gyrification caused by methamphetamine use is more significant the younger the drug abuse starts. Previous research has indicated that the same is true for cannabis use (Shollenbarger et al., 2015). Future studies interested in the effects of cannabis use on brain morphology and gyrification should aim to recruit a larger sample and record the frequency of use and age of onset to provide a more statistically reliable representation of the relationship between cannabis use and gyrification.

Conclusion

In conclusion, global and local gyrification do not appear to be associated with the presence of prolonged MAP or the symptoms of psychosis in this sample, diverging from the pattern seen in SSD and other primary psychotic disorders. The biopsychosocial model of MAP whereby gyrification serves as a neurodevelopmental biomarker for underlying psychosis risk is not strongly supported by the results of this study. Despite this, group membership was able to significantly account for variance in gyrification, with age and sex covariates also significantly accounting for group differences in gyrification. These group-based differences in gyrification appear most strongly in the temporal lobe, where MA participants have increased gyrification compared to controls and those with MAP, although this result was not significant. These results raise new questions about the impact of substance use on gyrification. In addition, there does appear to be a minimal association between temporal and occipital LGI values and total score on the PANSS measure for the MAP group and a minimal negative association between negative symptoms of psychosis and

gyrification in the frontal and temporal lobes, particularly the temporal pole. Alcohol and cannabis use were also minimally negatively associated with symptoms of positive psychosis, such as hallucinations and delusional thoughts. Although lack of statistical power due to a small sample size (n=18) does not provide significance to these results, they do raise new questions about the neurobiological systems underlying symptoms of psychosis in MAP and SSD. Looking beyond distinguishing between MAP and MA users, cortical gyrification demonstrated significant associations with age, alcohol use, cannabis use, and age of drug use onset, adding to previous research. These associations suggest that cortical folding patterns appear to be more affected by environmental factors than previously believed, raising new questions about the reliability of gyrification as a neurodevelopmental marker of disease risk. The results of this study raise questions about the neurodevelopmental basis of gyrification formation and the potential harm of drug-taking behaviour on brain structure and function, particularly at an early age.

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Appendix A

TITLE OF THE RESEARCH PROJECT:

Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis REFERENCE NUMBER: 340/2009 PRINCIPAL INVESTIGATOR: Dr Donald Wilson

ADDRESS: University of Cape Town, Dept of Psychiatry and Mental Health, Groote Schuur Hospital (J2), Anzio Road, Observatory 7925, Cape Town, South Africa CONTACT: E-mail:d.wilson@uct.ac.za, Phone: +27-21-404-2182, Fax: +27-21-448-8158

Dear Volunteer

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC) of the University of Cape Town, and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

This project is being run at the Department of Psychiatry, University of Cape Town. We aim to recruit a total of 60 participants over a period of 3 years.

What is this research study all about?

Background: The increasing use of methamphetamine (MA, also “tik” or “meth”) is a cause for concern for a number of reasons. On the personal level the chronic use of MA has been associated with brain damages resulting in potentially long-lasting mental health effects including confusion, impaired concentration and memory. Imaging studies have shown that MA use is associated with imbalances in the neurochemistry of the brain. Thus long-term abuse of “tik” or “meth” is associated with the development of paranoid, often violent psychotic states accompanied by auditory, visual and/or tactile hallucinations. MA abuse also has profound consequences on an interpersonal level, due to associated impairments in emotion regulation. For instance, aggression and hostility have been consistently identified in chronic users of MA and such emotional disturbances have been associated with abnormalities in functional and structural neuroanatomy.

Methods: Participants will have to complete questionnaires and a series of behavioural and cognitive tasks. Some of these will be used to determine whether MA abuse and MA-induced psychosis is associated with defects in social awareness and regulation of emotions. In addition, brain imaging techniques will be used to determine the effect of

MA abuse, with and without a history of psychosis, on brain structure and function. Specifically, structural magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) will be employed to investigate how brain structure and metabolism change in MA abusers in comparison to healthy controls. DNA analyses of blood samples will be conducted to examine whether specific genes account for structural and functional brain abnormalities after methamphetamine abuse and for increased vulnerability to psychosis.

In addition, associations between "tik" abuse and the disability of controlling emotions will be assessed. Participants will therefore perform a simple task (Affective Labelling task) measuring emotional processing as part of the functional MRI scan. This task will be used to assess differences in brain activation corresponding to impairments in regulating behaviour.

Procedures

If you agree to take part in the study and if you meet all of the conditions required for entering the study (assessed in a screening interview), you will complete the following 3 phases and procedures:

At your first visit the study will be explained and written consent to take part will be obtained. Your study investigator will ask you some questions about your psychiatric and neurological history and you will have to fill out several questionnaires. If you are eligible and agree to participate in the study you will be asked to attend the second testing session at the Cape Universities Brain Imaging Centre (www.sun.ac.za/cubic).

During the second testing day, you will be asked to complete behavioural tasks. Following completion of these tasks the brain scanning session, Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS), will take place.

During the third visit you will undergo neuropsychological testing including tasks about your memory, attention and risk taking behaviour.

It is estimated that none of the testing sessions should take more than 3-4 hours to complete.

The psychiatric interview will take place either at Valkenberg Hospital or in the Psychiatric department at Groote Schuur Hospital. Brain imaging will be conducted using a 3T Siemens Magnetom Allegra at CUBIC, Stellenbosch. Each scanning session will last approximately one hour. Structural and functional imaging data will be acquired. Stimuli for each cognitive-affective protocol will be computerized and displayed to you in the scanner via a screen display. The neuropsychological assessment, which will be computer based tests, will take place in the Psychiatric Department of Groote Schuur Hospital.

Urine screens will be performed on both days of testing to verify methamphetamine abstinence and to determine the degree of cannabis use, as well as for a pregnancy test (if you are female). You will have to pee in a cup for those tests. The results of those tests are not for legal medicine or police purpose, and will only be used for our study.

Blood samples will be collected for routine laboratory testing and for possible future gene and protein expression studies. Approximately 35ml (7 teaspoons) of blood will be drawn from your arm. We may need to contact you again to get another blood sample should we fail to get a DNA sample.

from your blood. Candidate polymorphisms identified to be associated with drug dependency or psychosis and possibly playing a role in explaining variance in the MRI results will be investigated later on. This process will take place at the Division of Human Genetics at the University of Cape Town.

Magnetic Resonance Imaging

With an MRI you can obtain very detailed images of organs and tissues throughout the body, even of the brain, as in our study. MRS provides a tool to investigate metabolites in the living brain. Both MRI and MRS testing cause no pain and the magnetic fields produce no known tissue damage of any kind.

The MRI and MRS examination are performed in a special room that houses the MR system or "scanner". You will be escorted into the room by a staff member of the MRI facility and asked to lie down on a comfortably padded table that gently glides you into the scanner. This is typically a large, tunnel magnet that is open at both ends, so you won't be completely enclosed at any time.

As the scan is done in a relatively confined space, occasionally people feel closed-in or frightened. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings. Another side-effect might be a tingling feeling in your teeth if you have metal fillings.

The most important thing for you to do is to relax and lie perfectly still during the time the imaging takes place. For the functional imaging you will be asked to perform some simple tasks of emotional processing and attention, which will enable the investigators to determine your brain function. During the structural and diffusion tensor imaging you will be able to close your eyes and rest. Given that the testing session will take one hour to complete, you might get sleepy or uncomfortable after a while, but you are asked to stay awake and not to move throughout the scanning.

A radiologist will operate the scanner from behind a window, and will be able to see and hear you during the scan. You will be able to communicate with the radiologist or the study assistant at any time using an intercom system. You will also be given an alarm call button to hold during the scan, which you can press to get attention.

The MR scanner may produce loud tapping or knocking noises at times during the testing, which is normal and should not worry you. Especially when the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. You will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this, we will give you some soft earplugs to put in.

MRI and MRS scans are commonly performed and a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team.

Why have you been invited to participate?

Three groups of participants will be included in this study: methamphetamine (MA) abusers with a history of psychosis, MA abusers without a history of psychosis and non-substance-abusing healthy control subjects. Each of the groups will consist of 20

participants. You may fit into one of these categories as assessed during your initial screening.

What will your responsibilities be?

The study investigator will be required to ask you about medications that you may be taking currently or that you may have taken recently. Your study investigator will explain to you which medications need to be stopped during the entire length of the study and how soon before you take part in the study these medications must be stopped.

Your doctor will also advise you on which prescription or over-the-counter medications or any other remedies or foods that you will be required to either stop or restrict your consumption of during the entire length of the study. This will include a restriction on the amount of alcohol that can be consumed.

At each visit you may be asked to complete questionnaires or tasks to check the status of your symptoms. These will measure your mood, emotional responses, trust, sociability and emotional resilience.

Please ensure that you are punctual at all times, as we are using specialized equipment during each of the sessions, for which costs are incurred. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.

Will you benefit from taking part in this research?

There are no direct benefits to you for participating in this study. However, you will be making an important contribution to this research that may benefit others in the future. We expect that the results of this study will help us understand the effects of methamphetamine on brain structure and function and how their abuse can lead to the development of psychosis.

Are there any risks involved in your taking part in this research?

There are no major risks involved in participation in this study. There will be several questionnaires, including some about past traumatic events that ask for information of a very personal and sensitive nature. This may cause some emotional discomfort.

Who will have access to your medical records?

Maintaining your confidentiality is important. Your personal information (for example your gender, age, the details of your medical conditions) and other information (the data collected by the investigators as part of the study) will be identified by a number (i.e. coded). Your name will not appear in any publications or reports produced from this study. The investigators will keep the information and the results collected about you in this study. This information about you will be kept in a secure place.

By agreeing to take part in this study, you will be allowing certain persons to see the information about you (both personal, including your name, and other information) held by the study doctor. You have the right to withdraw your consent to participate in this study at any time.

If you withdraw your consent to participate in this study no new information will be collected from you and added to existing data or to a database. Your information will be processed electronically (i.e. by a computer) or manually and analysed to determine the outcome of this study. Your information may/could be sent to regulatory

authorities and to the Ethics Committees. You have the right to ask the study doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any necessary corrections made to it.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

If you become ill or injured as a direct result of your participation in this clinical study, you will be referred for appropriate medical treatment. The University of Cape Town's insurance policy will cover the costs of such treatment. If you have any questions concerning the availability of compensation/medical care or if you think you have experienced a research-related illness or injury, contact details are below. Your legal right to claim compensation for injury where you can prove negligence is not affected.

If you have any questions about your rights as a research subject, you should contact the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), Tel: (021)4066492, Fax: (021)4066411.

If you have questions about this study you should first discuss them with your study doctor or the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), UCT.

Dr D. Wilson: (021)4042182 Dr H. Temmingh: (021)4403185

After you have consulted your doctor or the FHS HREC and if they have not provided you with answers to your satisfaction, you should write to the South African Medical Research Council at: Head Office Cape Town, Corporate Communications Office, Sarah Bok, PO Box 19070, Tygerberg, 7505, South Africa or Fax: (021)9380200.

Will you be paid to take part in this study and are there any costs involved?

All evaluations will be provided, hence there will be no costs involved for you or your medical aid, if you do take part in the study. You will be compensated for taking part in the study as your transport and meal costs will be covered with supermarket vouchers to exchange for food, amounting to R150.

Is there anything else that you should know or do?

You can contact the Committee for Human Research at (021)4066492 if you have any concerns or complaints that have not been adequately addressed by your study doctor. You will receive a copy of this information and consent form for your own records. Informed Consent Form for Study Participants

Title of the Research Project: "Neural correlates of deficits in affect regulation in methamphetamine abusers with a history of psychosis."

Declaration by participant

By signing below, I ……..……. agree to be interviewed and asked personal information as part of the above named study and that the information I give will be correct. Furthermore, I declare that:

I have read, or had read to me, the “Participant Information Leaflet and Consent Form” and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered. I understand that taking part in this study is voluntary and I have not been pressurised to take part. I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place) .....…..…….. on (date) ……...…….. 20
Signature of participant

By signing below, I ……..……. agree to have my blood taken for the proposed genetic tests as described in the “Participant Information Leaflet and Consent Form”.

Signed at (place) .....…..…….. on (date) ……...…….. 20

Signature of participant

By signing below, I ……..……. agree to undergo brain scans (MRI/MRS) as described in the “Participant Information Leaflet and Consent Form”.

Signed at (place) .....…..…….. on (date) ……..... 20

Signature of participant

By signing below, I ……..……. agree to Neuropsychological testing as described in the “Participant Information Leaflet and Consent Form”.

Signed at (place) .....…..…….. on (date) ……...…….. 20 .
Signature of participant

Declaration by investigator I (name) ……..……
declare that: I explained the information in this document to
……..

I encouraged him/her to ask questions and took adequate time to answer them. I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (place) .....…..…….. on (date) ……..... 20

Signature of investigator