Relationship between White Matter Changes and Aggression in Methamphetamine Dependence

by

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DECLARATION

I, Katharina Lederer, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background: Methamphetamine (MA) abuse is a growing problem in the world and especially in South Africa's Western Cape. Amphetamine-type stimulants have become the second most widely abused illicit drugs worldwide. Admission data from substance abuse treatment centres in the Western Cape show the fastest increase for any drug ever noted in the country in MA related admissions. MA has neurotoxic effects on the brain leading, amongst other effects, to white matter (WM) changes. Moreover, increased levels of aggression are commonly found in individuals with MA abuse. Although behavioural deficits are well described, the underlying mechanisms are still poorly understood. While previous studies have examined WM abnormalities relating to cognitive impairment, none have investigated associations between WM integrity in individuals with MA dependence and aggression.

Methods: Diffusion Tensor Imaging (DTI) was used to investigate WM changes in 40 individuals with MA dependence and 40 matched healthy control subjects. Aggression was measured with the Buss & Perry Questionnaire in 40 MA users and 36 controls. Two approaches to assess WM integrity in the brain were employed. First, whole brain voxel wise comparison across subjects using tract based spatial statistics (TBSS) in FSL was used. Fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity ($\lambda_{\parallel}$) and perpendicular diffusivity ($\lambda_{\perp}$) were compared between the two groups. Second, a region of interest (ROI) approach was used, which focused on three WM tracts in the frontal brain, commonly found to play a role in aggressive behaviour: (1) the genu of the corpus callosum (CC), (2) the cingulum and (3) the uncinate fasciculus.

Results: Mean aggression scores for Anger (p<0.001), Physical Aggression (p=0.032) and Total scores (p=0.021) were significantly higher in the MA group then in the controls. TBSS analysis revealed increased MD values in the right superior corona radiata in the MA group. ROI analysis showed increased MD (U= 439,5, p=0.00) and $\lambda_{\perp}$ (U=561,5, p=0.021) values in the genu of the CC in individuals with MA dependence. MD (U=541,5, p=0.012) values were also increased in the MA group in the right hippocampal region of the cingulum. There were no group differences in the uncinate fasciculus. None of the WM changes were significantly associated with aggression scores.

Conclusion: This study provides evidence of WM differences between abstinent individuals with MA dependence and healthy controls. Moreover, higher aggression levels in the MA group were found. The lack of significant association between WM changes and aggressive behaviour may reflect methodological issues in measuring such behaviour, or may indicate that the neurobiology of aggression is not simply correlated with WM damage but is more complex.

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I hereby also acknowledge that three quarters of the data set were already available when I joined the study. In the year of my participation I recruited 26 participants, was responsible for screening, organising and accompanying scanning sessions, updating data bases, and finally analysing the acquired DTI images.

I would like to thank everyone who worked on this study: the psychiatrists, the social workers, the technical assistants at the scanner and the driver.

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5-HT	Serotonin
AC-PC	Anterior Commissure – Posterior Commissure
ADC	Averaging Diffusion Coefficient
AMPH	Amphetamine
ANCOVA	Analysis of Covariance
ATS	Amphetamine-type stimulants
BET	Brain Extraction Tool
CC	Corpus Callosum
CgC	Cingulum Cingulate Gyrus Area
CgH	Cingulum Hippocampal Area
CSF	Cerebral Spinal Fluid
CTRL	Control
DA	Dopamine
DAT	Dopamine Transporter
DSM IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
FA	Fractional Anisotropy
FDR	False Discovery Rate
FDT	Functional MRI of the Brain Diffusion Toolbox
FMRI	functional Magnetic Resonance Imaging
FMRIB	Functional MRI of the Brain
FNIRT	Functional MRI of the Brain Nonlinear Image Registration Tool
FSL	Functional MRI of the Brain Software Library
GLM	General Linear Model
GM	Grey Matter

HREC	Human Research Ethics Committee
JHU	John Hopkins University
LH	Left Hemisphere
LTD	Long-term Depression
LTP	Long-term Potentiation
MA	Methamphetamine
MANOVA	Multivariate Analysis Of Variance
MD	Mean Diffusivity
MDMA	3,4-Methylenedioxymethamphetamine
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NcA	Nucleus Accumbens
OFC	Orbito Frontal Cortex
PET	Positron Emissions Tomography
PFC	Prefrontal Cortex
RH	Right Hemisphere
ROI	Region of Interest
SCID	Structures Clinical Interview of DSM IV Disorders
SPSS	Statistical Package for the Social Sciences
TBSS	Tract-Based Spatial Statistic
TCI	Transcallosal Inhibition
TFCE	Threshold-Free Cluster Enhancement
THC	Tetrahydrocannabinol
TMS	Transcranial Magnetic Stimulation
UNODC	United Nations Office on Drugs and Crime
VBM	Voxel Based Morphometry

VLPFC	Ventrolateral Prefrontal Cortex
VMPF	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area
WCST	Wisconsin Card Sorting Test
WM	White Matter
$\lambda_{\parallel}$	Parallel Diffusivity
$\lambda_{\perp}$	Perpendicular Diffusivity

Introduction

Worldwide, methamphetamine (MA) abuse has accelerated dramatically. As a result of its easy and inexpensive production, amphetamine-type stimulants (ATS) have become the second most widely abused illicit drug worldwide (United Nations Office on Drugs and Crime [UNODC], 2012). The newly released World Drug Report (UNODC, 2014) stated that globally a total of 144 tons of ATS were seized in 2012.

MA abuse in South Africa's Western Cape has also shown an enormous increase in the last decade. Worldwide, South Africa ranks on place three of ATS prevalence. Furthermore, the UNODC reports an increase in MA and heroin abuse in South Africa with other drugs being stable in 2012. Simbayi et al. (2006) showed that 18% of men and 12% of women in a township in Cape Town admitted having tried MA at least once. MA was also reported the second most abused drug (after cannabis) among treatment patients in Cape Town younger than 20 years (Plüddemann et al., 2010). Admission data from substance abuse treatment centres in in that area during a four-year period (2002–2006) state the proportion of patients reporting MA as their primary substance of abuse show a steady increase from 0.3% to 42.3%. This represents the fastest increase in admissions for any particular drug ever noted in the country (Plüddemann, Myers & Parry, 2008) with numbers declining only minimally to 35 % in 2008 (Plüddemann et al., 2013).

MA is a highly addictive synthetic psychostimulant, which can cause serious general and mental health problems, including psychosis, depression, cognitive impairment, anxiety and violent behaviour (Cherner et al., 2010; Darke et al., 2008; McKetin et al., 2008). MA, also known by its street name 'tik', is commonly smoked in a glass pipe or similar device but can also be injected, swallowed or sniffed. Immediate effects include euphoria, confidence, physical activity, decreased appetite, arousal and sleeplessness (Darke et al., 2008; Panenka et al., 2013; Romanelli & Smith, 2006).

Drug abuse is a massive burden for society. The United States spent estimated 193 billion US$ in 2007 for health and legal costs, loss of productivity, incarcerations and other consequences of illegal drug use (National Drug Intelligence Centre, 2011). Furthermore, for communities MA abuse is a social burden. Several studies report on the social impact on children and families, like child neglect, poor birth outcomes, and school dropouts

(Plüddemann, Louw & Leggett, 2004; Sommers & Baskin, 2006; Watanabe-Galloway et al., 2009). Additionally, Haight et al. (2010) showed that children growing up in families involved in MA abuse are at a higher risk to develop aggressive behaviour, depression, and mental health problems. Individuals with MA abuse also engage more likely in risky sexual behaviour leading to sexually transmitted infections like HIV (Plüddemann et al., 2013). Taken together, MA abuse has a negative impact on several levels, the personal, the communal, and the state level.

One of the serious consequences of MA use, I am going to concentrate on in this work, is the increased levels of aggression in individuals with MA dependence. It is widely reported that individuals with MA dependence show more aggressive behaviour (Boles & Miotto, 2003; Booth et al., 2006; Cohen et al., 2003; Lapworth et al., 2009; Payer et al., 2011; Plüddemann et al., 2010; Sommers & Baskin, 2006; Zweben et al., 2004) leading to domestic abuse, increased crime rates and corruption (Watt et al., 2014). 80% of women enrolled in a MA treatment program reported domestic violence from their partner and 57.6% stated that they have been sexually abused (Cohen et al., 2003). Cartier, Farabee and Prendergast (2005) reported, “methamphetamine use was significantly predictive of self-reported violent criminal behaviour and general recidivism”. Additionally, Plüddemann et al. (2010) showed in a study with 1561 high school students in Cape Town that MA abuse was significantly related to higher aggressive behaviour.

The second effect of MA dependence, that I am going to investigate in this thesis, is the neurotoxicity of the drug, leading to neuronal cell damage and subsequently to structural changes in the brain (Cadet & Krasnova, 2009; Davidson et al., 2001; Riddle et al., 2006). These changes at the cell level result in changes of fibre connections in neural circuits. Recent imaging studies have described several white matter (WM) changes in MA abuse as well as their association with problems in cognitive control (Alicata et al., 2009; Chung et al, 2007; Kim et al., 2009) and psychiatric disorders (Tobias et al., 2010). Diffusion tensor imaging (DTI) is an optimal tool for investigating WM changes because it can measure WM integrity in-vivo based on the diffusion of water molecules. There are only a limited number of DTI studies in MA abuse though. Previous studies showed impaired WM integrity in aggressive and impulsive behaviour, psychiatric disorders, which show increased levels of aggression and in substance dependence (Hoptman et al., 2002; Moeller et al., 2001; Saxena et al., 2012; Zhang

et al., 2014). However, the relationship between WM changes in MA abuse and behavioural deficits are still unclear.

Based on this background the rationale of this study was to delineate the relationship between WM changes and aggression in individuals with MA dependence. Therefore, DTI data from participants of an ongoing MA imaging study at the University of Cape Town were analysed and correlated with the scores from a self-report Aggression Questionnaire (Buss & Perry, 1992).

The thesis will comprise four further chapters, as follows:

The first chapter contains a literature review, where I will explain DTI, which was used in this study to delineate the WM changes in MA dependence. I will then summarize studies conducted in MA abuse concentrating on the neurobiological effects of MA consumption as well as neuroanatomical regions involved as shown by several neuroimaging studies. In the last section, I will focus on aggression, reviewing what is known about the neurobiology and the neural correlates of aggressive behaviour. Ending this chapter, I will discuss my hypothesis and objectives.

The second chapter contains an introduction to DTI analysis using the functional MRI analysis programs of the Brain Software Library (FSL). There, I will explain the recruitment process and questionnaires used in this research. I will also highlight the statistical procedures for analysing the results.

A third chapter will state the results of this research. The fourth chapter summarizes these results and places them back into the context of WM differences in MA dependence and its relevance for behavioural changes. I will also suggest ways in which research can be continued to build even further upon our understanding of how WM changes relate to behaviour. Possible limitations to the study will also be discussed.

1. Literature Review

1.1 Diffusion Tensor Imaging

WM fibre pathways connect cerebral cortical areas with each other and with subcortical structures. Thereby, they allow communication between different brain regions building the neural network that subserves sensorimotor function, intellect and emotion. Abnormalities in WM have been associated with a wide spectrum of emotional disturbances (Filley, 1998), cognitive impairment (Alicata et al., 2009; Chung et al., 2007; Kim et al., 2009) and psychiatric disorders (Saxena et al., 2012; Sundram et al., 2012; Tobias et al., 2010; Zhang et al., 2014). In this section, it will be explained how diffusion tensor imaging (DTI) can be used to investigate microstructural WM changes.

DTI is a sensitive brain imaging technique, which relies on the anatomical structure of WM in the brain. Cerebral WM consists of axons coated with myelin and covers 40-50% of the adult human brain (Filley, 2005). The fibre pathways create a grid with axons going in mainly three directions and almost crossing at right angles (Wedeen et al., 2012). DTI provides the possibility of following and investigating these fibre pathways non-invasively and enables us to examine the anatomical connectivity of the brain.

DTI is an optimal tool for investigating microstructural WM changes in-vivo. It is based on the Brownian motion effect of water. In isotropic conditions, like in cerebrospinal fluid (CSF) or grey matter (GM), water molecules diffuse randomly in any direction. In a nerve fibre, however, the axonal membrane and the myelin sheet restrict movement, resulting in a main movement direction along the nerve fibre instead of perpendicular to it (Basser et al., 1994; Beaulieu, 2002). The diffusion of water is measured in multiple directions to calculate the three mean movement directions resulting in a 3D image. The intensity of each image element (=voxel) reflects the water diffusion rate (Mori & Zhang, 2006). If we think of each voxel as an ellipsoid shape each axis of the ellipsoid will represent a direction of diffusion characterized by the *eigenvectors* and the radius by the *eigenvalues* λ_1, λ_2 and λ_3 (Taylor et al. 2004). In anisotropic tissue the main direction of water diffusion is represented by the largest diffusion value λ_1, describing the parallel diffusivity ($\lambda_\parallel$) along the nerve fibre. λ_2 and λ_3 can be used to calculate the restricted perpendicular diffusivity ($\lambda_\perp$) of water molecules by taking the mean of the two values ($\lambda_\perp = (\lambda_2 + \lambda_3)/2$). Altered microstructure of WM fibre tracts due to pathology or physiological changes, influence the magnitudes of the eigenvalues (Alexander et al., 2007).

From the three diffusivities, we can calculate the fractional anisotropy (FA), which is a measure of the restricted movement of water molecules in a nerve fibre. FA is calculated as the normalized standard deviation of λ_1, λ_2 and λ_3 in every voxel. Previously reported decreases in FA were interpreted as damages to the myelin sheet, the axonal fibre, as oedema, or inflammation (Cercignani et al., 2001). FA can therefore be used to describe WM integrity (Hasan, Alexander & Narayana, 2004; Le Bihan et al., 2001) and is the most widely used measure in DTI brain research (Assaf & Pasternak, 2008). FA values can be between one and zero, being high (1) in WM and low (0) in GM and CSF where there is no main directional diffusion.

Another measurement used to describe WM changes includes the mean diffusivity (MD) which is a direction independent measure of overall diffusion of water molecules in each voxel. MD - sometimes called the averaging diffusion coefficient (= ADC) - is calculated as the average of the three eigenvalues ($MD= (\lambda_1+ \lambda_2 + \lambda_3)/3$) (White, Nelson and Lim, 2008). I use MD instead of the term ADC because it can easily be confused with the apparent diffusion coefficient. Increases in MD might be due to a decrease in membrane density and therefore less restriction in water diffusion (Beaulieu, 2002; Douaud et al., 2011).

1.2 Methamphetamine

MA is a white, crystalline, odourless powder, which, in South Africa, is commonly smoked in a glass pipe. MA abuse states a serious problem for general health as it can cause extreme weight loss, dental problems, insomnia, or high blood pressure increasing the risk for strokes (Darke et al., 2008; Panenka et al., 2013; Romanelli & Smith, 2006; Yen et al., 1994). Mental health problems include anxiety, paranoia, cognitive impairment, depression, and aggressive behaviour (Boles & Miotto, 2003; Booth et al., 2006, Cherner et al., 2010; Darke et al., 2008; McKetin et al., 2008). Additionally, MA can cause neural cell damage leading to structural changes in the brain. How the cell injuries occur will be covered in the next section.

Neurobiology of methamphetamine

A recent review by Halpin, Collins & Yamamoto (2014) summarizes the neurotoxic effects of MA. Acute MA administration increases extracellular dopamine (DA) and serotonin (5-HT) levels. DA levels increase through release of DA vesicles into the synaptic junction and by blocking presynaptic dopamine transporters (DAT). This inhibits the reuptake of DA from the presynaptic nerve resulting in higher DA concentrations in the synaptic junction. In addition, glutamate increase in the striatum was detected (Mark et al., 2004) causing rises in intracellular calcium levels which activates calcium-dependent proteolytic enzymes, free radicals and nitrite oxide resulting in cell damage and apoptosis (Nicholls, 2004). Chronic use of MA however is followed by a depletion of DA and 5-HT by axonal degeneration and axon terminal damage due to chronic oxidative stress, direct toxicity of MA and down-regulation of receptors (Cadet et al., 2007).

Long-term effects, such as DA and 5HT axon terminal damage, were reported to last over two years (Volkow, 2001), specifically in the striatum, hippocampus and the prefrontal cortex (PFC) (Seiden et al., 1988; Wagner et al., 1980). Neuronal cell death in the striatum and PFC was mainly ascribed to GABA interneurons via mitochondrial and DNA damage as well as endoplasmic reticulum stress (Cadet, Jayanthi & Deng, 2005; Kuczenski et al., 2007).
Other mechanisms contributing to neuronal cell death include oxidative stress, altered cell metabolism and inflammation (Quate et al., 2004; Sprague, Everman & Nichols, 1998; Thomas et al., 2004). Mechanisms of the latter are not well understood, but thought to be activated through microglial activation in striatum, cortex and hippocampus (Kuhn, Francescutti-Verbeem & Thomas, 2006; Thomas et al., 2004). The authors conclude that

several persistent mechanisms interact with each other and contribute to MA induced cell and axon damage.

Dopamine, the reward system and addiction

Addiction is a state of compulsive drug use despite serious negative consequences (Cami & Farré, 2003). In the DSM-IV as well as in our study, criteria for drug dependence are as follows (American Psychiatric Association, 2000):

a. Tolerance (marked increase in amount; marked decrease in effect);
b. Characteristic withdrawal symptoms; substance taken to relieve withdrawal;
c. Substance taken in larger amount and for longer period than intended;
d. Persistent desire or repeated unsuccessful attempt to quit;
e. Much time/activity to obtain, use, recover;
f. Important social, occupational, or recreational activities given up or reduced;
g. Use continues despite knowledge of adverse consequences

Dependence is diagnosed when three or more criteria are met in a 12-month period. Criteria for MA abuse on the other hand are fulfilled when one of the following criteria is met in a 12-month period (American Psychiatric Association, 2000):

a. Recurrent use resulting in failure to fulfil major role obligation at work, home or school
b. Recurrent use in physically hazardous situations
c. Recurrent substance related legal problems
d. Continued use despite persistent or recurrent social oar interpersonal problems caused or exacerbated by substance

Considerable research has been done and a series of theories about the brain circuits and neurotransmitter involved in drug addiction have been proposed. It is clear that DA is not the only neurotransmitter playing a role but most certainly it is a pivotal one. Researchers agree that DA is not just the ‘reward’ hormone but that it provides things with ‘importance’ or ‘salience’. In animal studies, it was shown that primates could still “like” a substance in the absence of DA but that they would not change their behaviour to obtain such a substance (Hyman, Malenka & Nestler, 2003). Berridge & Robinson (1995) stress the difference between ‘liking’ and ‘wanting’ in drug addiction. The authors propose that DA release by drug

intake causes sensitization to neural areas associated with 'wanting' but not 'liking'. Therefore, they conclude that addiction leads to a dissociation of 'wanting' and 'liking' – 'wanting' becoming more and more prominent while 'liking' is declining.

Structural parts of the brain involved in drug addiction are, amongst others, the ventral tegmental area (VTA), the nucleus accumbens (NcA), the PFC and the amygdala (Everitt et al., 2008; Goldstein & Volkow, 2002). The enjoyable effects of MA are assumed to be caused by an increase of DA in the NcA (Keleta & Martinez, 2012; Piazza & Deroche-Gamonet, 2013) – the same as for many other drugs of abuse, or natural rewards like food intake or sexual behaviour (Everitt, Dickinsen & Robins, 2001). The drug therefore reinforces the natural reward system in the brain (Piazza & Deroche-Gamonet, 2013).
DA neurons in the ventral tegmental area (VTA) project to the NcA (=ventral Striatum) as well as the amygdala and hippocampus, building the mesolimbic pathway which plays a role in drug-related memories and conditioned responses as well as reward (Koob & Bloom, 1988). The mesocortical pathway is made by neurons connecting the VTA to the PFC. The NcA can be divided into a core and a shell region. The shell has strong connections to emotion regulating areas and responds to novel rewarding stimuli. The PFC, especially the anterior cingulate cortex and the orbitofrontal cortex (OFC), are involved in valuating reward and inhibitory control over behaviour (Hyman, Malenka & Nestler, 2003).

The transition from drug use to addiction might be regulated by reward-related learning processes (Hyman, Malenka & Nestler, 2003). This theory is supported by the experience that the drug is continuously taken even if the pleasurable effect is long gone (Volkow, Fowler & Wang, 2004). Long-term potentiation (LTP) and long-term depression (LTP) play an important role in learning and memory processes. LTP and LTD lead via neuroplasticity to either a strengthening or a reduction of synaptic connections, and hence, translate into potentially long-term neuronal changes. These changes have been demonstrated to occur in reward related brain areas as a consequence of drug use (Hyman, Malenka & Nestler, 2003; Nestler, 2001). Furthermore, DA enhances LTP in hippocampal-prefrontal cortical synapses (Gurden, Takita & Jay, 2000) and therefore strengthens learning processes related to the drug.

As a consequence of these learning-processes changes in neural circuits can be observed. Volkow, Fowler & Wang (2004) focus in their review on imaging studies in individuals with drug abuse (mainly cocaine and ATS) and show disrupted neural circuits in drug related areas

such as “reward/saliency, motivation/drive, inhibitory control/disinhibition, and memory/conditioning”. The authors point out reduced DA activity in drug abuse in the PFC, especially in the OFC and the anterior cingulate gyrus, in positron emissions tomography (PET) studies. Impaired control of the PFC over behaviour could contribute to the uncontrolled, disinhibited drug use seen in individuals with drug abuse (Volkow et al., 2002).

Summarizing the neurobiological effects of MA on the brain and its relevance for addiction, acute MA administration leads to an increase of DA levels, but chronic use results in a depletion of DA. Additionally, DA plays an important role in the brain reward system, which is strongly linked to addiction. MA causes cell damage through multiple mechanisms leading to structural changes in the brain. These changes at the cell level may result in changes in neural circuits and therefore changes in behaviour.

Neuroimaging in methamphetamine abuse

Neuroimaging allows researchers to investigate the brain in vivo. Different imaging techniques like magnetic resonance imaging (MRI) and spectroscopy (MRS), PET and functional MRI (fMRI), have been used to identify structural brain changes in chronic MA abuse and dependence but just a limited number used DTI to examine WM integrity. In this section, I summarize the results of multiple brain imaging studies investigating the effects of MA on the brain. First, I will give an overview of the results of structural MRI studies in MA abuse. Then I will focus in more detail on the results of DTI studies in MA dependence.

Methamphetamine and MRI

A substantial number of studies focused on GM volume changes in MA abuse and dependence. The frontal lobe is repeatedly found to exhibit lower GM volumes in individuals with MA abuse (Kim et al., 2006; Nakama et al., 2011; Schwartz et al., 2010) as well as in users of other ATS’s (amphetamine and 3,4-methylenedioxymethamphetamine (MDMA)) (Daumann et al., 2011), compared to healthy controls. Additional findings are lower GM density or smaller GM volume in MA abuse in the insula (Nakama et al., 2011; Schwartz et al. 2010), the parietal lobe (Jernigan et al. 2005), cingulate gyrus, paralimbic and limbic cortices, and the hippocampus (Thompson et al., 2004) as well as in the temporal lobe in ATS abusing individuals (Bartzokis et al., 2000). Another consistent finding is higher GM volume in the striatum in MA abuse (Chang et al., 2005; Jernigan et al., 2005) and other stimulant-abusing individuals (cocaine) (Jacobsen et al., 2001).

In addition, WM structural changes have been observed in MA dependence. Thompson et al. (2004) found increases in total WM volume, especially in temporal areas surrounding the hippocampus and occipital areas, in 22 individuals with a history of MA dependence. Bae et al. (2006) found frontal lobe and periventricular WM hyperintensities, which were more prominent in male then in female individuals with MA dependence. These findings were replicated by Alaee et al. (2014) who similarly found frontal lobe WM hyperintensities in individuals with MA dependence.

A study by Mackey et al. (2014) in 165 occasionally ATS using college students found that even occasional use of ATS can change brain structure. They showed higher grey matter (GM) volume in the left anterior ventral putamen and lower GM volume in the right dorsolateral cerebellum and right inferior parietal cortex in the ATS using students. Moreover, the authors could show a correlation between mid-insula and ventromedial PFC volumes and lifetime amount of ATS use. These findings show that occasional ATS use may already lead to brain changes, although they differ from findings in chronic drug use as discussed below.

The pathophysiology of brain volume decrease or increases in GM and WM is still unclear. Volume loss might be due to shrinkage of large neurons as seen in the aging brain (Terry, DeTeresa & Hansen, 1987). As outlined above, the neurotoxic effects of MA are well studied and cell damage and cell death may be due to dopaminergic and serotonergic neurotoxicity and synaptic damages. Inflammation on the other hand can trigger reactive gliosis and might be the cause for volume increases seen in WM regions (Schwartz et al., 2010; Sekine et al., 2008; Thomas et al., 2004).

DTI and methamphetamine dependence

There is only a small body of literature on WM changes in individuals with MA dependence, using DTI. Recent studies have described several WM changes in MA dependence as well as their association with problems in cognitive control (Alicata et al., 2009; Chung et al., 2007; Kim et al., 2009).

The first study published on DTI in individuals with MA dependence was undertaken by Chung et al. (2007). The study investigated the relationship of decreased frontal WM integrity and impairment in frontal executive function. The authors showed that individuals with MA

dependence had significantly lower FA values in bilateral frontal WM at the anterior commissure–posterior commissure (AC–PC) plane, relative to the control group. Executive functioning was measured with the Wisconsin card-sorting test (WCST) showing that individuals with MA dependence had more total, perseveration and non-perseveration errors relative to healthy comparison subjects. Correlational analyses found a relationship between decreased FA values of frontal WM and decreased WCST performances in individuals with MA dependence.

Subsequently, Kim et al. (2009) measured FA and eigenvalues in the corpus callosum (CC) and likewise, correlated their findings to the WCST. They found significantly reduced FA in the genu but not in the splenium of the CC in individuals with MA dependence compared to controls. The total WCST error score correlated negatively with FA and positively with the perpendicular diffusion coefficient ($\lambda_{\perp}$), but not with the parallel diffusion coefficient ($\lambda_{\parallel}$). Both of these studies support the idea that decreased frontal WM integrity may underlie poor frontal executive function observed in individuals with MA dependence.

Another task examining cognitive control, the Stroop selective attention task, was used in a study by Salo et al. (2009) to study the relationship between behavioural regulation and WM microstructure within the callosal region. They measured FA, ADC (=MD) and eigenvalues in the splenium and genu of the CC. The authors showed greater Stroop reaction time interference in individuals with MA dependence compared with healthy controls. In addition, FA within the genu but not splenium correlated significantly with measures of cognitive control in individuals with MA dependence but not in controls. However, their FA values in the genu of the CC did not survive correction for multiple comparisons.

Alicata et al. (2009) also showed lower FA in right frontal WM and additionally, higher ADC in the left caudate and bilateral putamen in individuals with MA dependence compared to controls. Using the Addiction Severity Index (ASI) they describe a link between drug measurements, like “earlier initiation of MA use, greater daily amounts, and a higher cumulative lifetime dose”, and increased ADC values in the left putamen. ADC in the right putamen was also associated with greater daily MA amounts and a higher cumulative lifetime MA dose. As previously discussed (Alexander et al., 2007) higher ADC can be interpreted as increased water content in each voxel as occurring in inflammation, or damage to the myelin sheet. In conclusion, the higher ADC in the basal ganglia noted by Alicata et al. could be due

to more damage in this region, associated with younger age of first MA use and greater MA usage.

Tobias et al. (2010) investigated the relationship of WM abnormalities with mood and psychiatric symptoms. They used the Beck Depression Index (BDI) score as a measure of depressive symptoms and the Brief Symptom Inventory (BSI) Positive Symptom Total score as a global measure of psychiatric symptoms. FA was measured at eight regions in the CC and at four inferior-superior levels parallel to the AC–PC plane (AC= anterior commissure, PC= posterior commissure). Their findings included lower FA in right prefrontal WM above the AC–PC plane, in the genu corpus of the CC, right midcaudal superior corona radiata and in right perforant fibres in MA dependence compared to controls. Decreased FA in left midcaudal superior corona radiata was correlated with BDI and BSI scores within the MA group.

In conclusion, several DTI measures indicating impaired WM integrity have been shown to correlate with diminished frontal executive function (Chung et al., 2007; Kim et al., 2009; Salo et al., 2009), addiction severity (Alicata et al., 2009) as well as depressive symptoms and generalized psychiatric dysfunction (Tobias et al., 2010) in MA dependence. Damage to the frontal WM and the genu of the CC in particular may underlie the cognitive and behavioural impairments observed in individuals with MA dependence.

1.3 Aggression

MA abuse has been strongly linked to aggressive behaviour (Boles & Miotto, 2003; Booth et al., 2006; Cartier, Farabee & Prendergast, 2005; Cohen et al., 2003; Payer et al., 2011). Aggression – as defined by Buss (1961)-is a "response that delivers noxious stimuli to another organism". Geen (2001) gives a more extensive explanation: "Aggression is the delivery of an aversive stimulus from one person to another, with intent to harm and with an expectation of causing such harm, when the other person is motivated to escape or avoid the stimulus". In my thesis, I will use the term aggression as most psychologists define it - simply as an act intended to harm others (Baron & Richardson 1994; Anderson & Bushman, 2002).

After presenting different forms of aggression, I will depict the relationship between MA and aggression and illustrate why it is important to investigate the possible mechanisms of aggressive behaviour in MA abuse. To explain the underlying neurobiology of aggression, I will then return to the discussion about the role of DA and 5-HT in the brain and describe how MA influences their concentration levels. Concentrating on the structural brain changes that are linked to aggressive behaviour, I will then emphasize that MA causes damage in similar regions important for emotion regulation particularly in the PFC, the CC and parts of the limbic system.

Forms of aggression

There are many ways to distinguish forms of aggression. A widely accepted form and the one I am going to focus on in my thesis is the differentiation between *reactive* and *instrumental* aggression. Instrumental aggression, also referred to as proactive or premeditated aggression, is a goal-related, offensive form of aggression. The drive for this form of aggression is the reward the perpetrator receives after the planned aggressive act (Vitaro, Brendgen & Baker, 2006). Alternatively, as Barret & Felthouse (2003) explain it: the "assault [is] carried out to benefit the attacker in some way".

Reactive aggression on the other side, also known as the affective/emotional form, is usually triggered by a threat or frustration (Tuvblad et al., 2009). It is immediate (impulsive) and unplanned and goes mostly hand in hand with an expression of anger. Impulsivity is closely related to this form of aggression defined as ''an individual's predisposition toward rapid,

unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or others'' (Moeller et al., 2001).

Barret & Felthouse (2003) state that impulsivity is a risk factor for reactive aggression. Individuals with MA abuse tend to have decreased behavioural inhibition (Kim et al., 2005; Davidson et al., 2001; Lapworth et al., 2009). Lapworth et al. (2009) found a link between impulsivity and hostility in MA users. They showed that impulsivity has a moderating role in the relationship of MA use and hostility. Increased dependence on MA correlated with higher levels of impulsivity and was associated with increased hostility. Consecutively, Schwartz et al. (2010) found higher impulsivity scores in MA users then in control.
Therefore, the major form of aggression in MA abuse suggests to be reactive aggression rather than instrumental.

Methamphetamine and aggression

Previous animal studies on the effects of MA on aggressive behaviour first showed mixed results. On the one hand, Crowley et al. (1972) noticed more fighting in MA administered mice, but others did not (Miczek and O'Donell, 1978). An animal study by Sokolov, Schindler & Cadet (2004) showed that chronic MA administration to mice is associated with more aggressive and hostile behaviour but not in single exposure with MA.

Numerous human studies show increased aggressive behaviour in individuals with MA abuse and dependence (Lapworth et al., 2009; Payer et al., 2011; Plüddemann et al., 2010; Sommers & Baskin, 2006; Zweben et al., 2004). Plüddemann et al. (2010) found in a study with 1561 high school students from Cape Town that "methamphetamine use in the past year was significantly associated with higher aggressive behaviour scores". Only a few studies list the causes of violent behaviour as Sexton et al. (2009) do: "disputes over MA or its use, as well as paranoia, ill-tempers, and hallucinations during MA binges". This emphasises how important it is to understand the mechanisms underlying aggressive behaviour in MA abuse.

Nevertheless, the precise nature of the relationship between MA abuse and aggression is still unclear. Payer, Liebermann and London (2011) questioned if MA abuse might not be the cause but the result of aggressive behaviour and impulsivity. Sommers, Baskin & Baskin-Sommers (2006) on the other hand found that half of all individuals with MA abuse who showed aggressive behaviour had not committed an aggressive act prior to using MA. It is

also possible that pre-existing aggressive and impulsive personality traits exacerbate by the use of MA. Another theory by Dawe et al. (2009) is that MA use is not the direct cause of making subjects aggressive, but for example, that other factors such as the sleep deprivation caused by the psychostimulant are more relevant. Another widely discussed hypothesis is that positive psychotic symptoms, particularly paranoia and suspiciousness, precipitated by the use of MA, can stimulate aggressive behaviour (Lapworth et al., 2009). Clearly, a seemingly hostile environment would trigger aggression as well. Lapworth et al. (2009) found that patients who had severe positive psychotic symptoms and high impulsivity were the most hostile.

Studies have shown that individuals with MA dependence have difficulties recognizing angry faces. Facial expressions are a social cue to change behaviour in dangerous situations (Payer et al., 2007). Hoptman (2003) argues that individuals with deficiencies in fear processing (not being able to process social fearful stimuli like angry faces) may be unable to avoid dangerous situations or withdraw themselves of such. The amygdala plays a key role in recognizing facial expressions and in fear processing (Costafreda et al., 2008; Davis, 1997; Hoptman, 2003; Sergerie et al., 2008). The inferior PFC has strong connections to the amygdala and modulates its activation (Davidson, Putnam & Larson, 2000; Peters & Sethares, 2002). Hoptman (2003) concludes that abnormalities in the inferior frontal cortex might change its modulatory role over the amygdala and result in impaired fear processing. Likewise, Davidson, Putnam & Larson (2000) state that lesions in the OFC as part of the PFC produce syndromes characterized by impulsivity and aggression.

Applying these findings to the relationship between MA and aggression, structural MRI studies have shown extensively that the PFC is affected by MA use (Alaee et al., 2014; Bae et al., 2006; Kim et al., 2006; Mackey et al., 2014; Nakama et al., 2011; Schwartz et al., 2010). MA and its structural brain changes might therefore play a role in the emergence of aggression.

These studies are an example of many theories and findings about the relationship of MA and aggression but there is not yet consistent agreement. Furthermore, there are no studies investigating WM changes in MA dependence relating to aggression.

Neurobiology of aggression

The neurotransmitter DA plays an important role in reward related behaviour, motivation, cognition and movement (Arias-Carrion & Poeppel, 2007). As discussed in the neurobiology of MA abuse section, DA additionally is related to addiction. 5-HT, which is thought to play a role in depression given that serotonin-reuptake inhibitors are effective in this condition, also has significance in aggression. Here I am going to highlight interactions between DA and 5HT and their link to aggressive behaviour. Of course, there are other hormones like testosterone, which also play an important role in mediating aggressive behaviour, but for lucidity, I will focus on DA and 5-HT.

Impulsive aggression is associated with low levels of 5-HT and 5-HT-receptor density (Davidson et al., 2001; Sekine et al., 2006; Seo, Patrick & Kennealy, 2008). As outlined above, chronic MA administration is followed by nerve terminal damage resulting in low 5-HT levels in MA abuse. It has been demonstrated that 5-HT has an inhibiting effect on aggression (Volavka, 1999) and lower serotonin levels correlated with more aggressive behaviour (Coccaro, 1989; Sekine et al., 2006). Moreover, Sekine et al. (2006) found an inverse correlation between 5-HT receptor density and aggressive behaviour, which also correlated with the duration of MA abuse. In addition, low levels of 5-HT could be correlated with decreased activation of the anterior cingulate cortex in individuals with impulsive aggressiveness (Frankle et al., 2005).

Interestingly, the PFC has a high density of serotonin type 2 receptors (Biver et al., 1996) and 5-HT increases activity in the PFC (Mann et al., 1996). Seo, Patrick & Kennealy (2008) reviewed studies investigating this link between hypodynamic 5-HT states and decreased PFC activation in aggressive individuals. They concluded that "decreased serotonergic neurotransmission in brain regulatory systems such as the PFC and the anterior cingulate cortex may be a major neurobiological deficit that leads to inhibitory dysfunction and aggressive behaviours". I will focus on the anatomical regions involved in aggression in the next section.

In contrast, high DA levels are consistently associated with elevated impulsive aggression. Mice and human study findings support a direct link between high DA and aggressive behaviour (Anstrom, Miczek & Budygin, 2009; Couppis & Kennedy, 2008; Ferrari et al., 2003; Harrison, Everitt & Robben, 1997). An intervention study by Couppis et al. (2007) found that blocking DA receptors decreased aggressive behaviour in mice. Buckholtz et al. (2010)

scanned 32 healthy volunteers with PET after administering a low dose of amphetamine (AMPH) or a placebo. The AMPH administration resulted in an increase of DA in the striatum. In addition, higher scores on the Barrett Impulsiveness scale were found in the AMPH group with AMPH-induced DA release.

5-HT levels have a strong interaction with DA levels. Daw et al. (2002) and Wong et al. (1995) proposed a reciprocal interaction between 5-HT and DA supporting the findings above. As mentioned before Seo, Patrick & Kennealy (2008) proposed a model where dysregulation of 5-HT (low) and DA (high) especially in the PFC predispose individuals to impulsive aggression. They went even further and suggested "Substance abuse associated with impulsive aggression is understood in the context of dopamine dysregulation resulting from serotonergic deficiency".

Neuroanatomy of aggression

Asymmetry Model

It has been posited that the right and the left-brain hemispheres play different roles in emotion and behaviour. Tullett, Harmon-Jones & Inzlicht (2012) showed in an EEG study that higher right frontal activation predicts empathic behaviour. Previous studies showed that right frontal asymmetry correlated with stronger negative affect and people are more likely to develop depression (Henriques & Davidson, 1990; Nusslock et al., 2011; Schaffer, Davidson & Saron, 1983; Tomarken et al., 1992; Wheeler et al., 1993). The left side of the brain on the other hand is playing an important role in happiness and anger (Coan, Allen & Harmon-Jones, 2001; Davidson, Schaffer & Saron, 1985; Harmon-Jones & Allen, 1998).

One idea is that of an approach- left brain- and avoidance –right brain- motivation model of frontal asymmetric activation. *Approach motivation* is explained by Schutter & Harmon-Jones (2013) by a motivation to 'experience a positive outcome' while *avoidance motivation* seeks 'not to experience a negative outcome'. In their very recent review, they discussed EEG studies, which link left brain dominance to anger and aggressive behaviour. A review by Hecht (2011) shows that left-brain dominance is found in psychopaths and Keune et al. (2012) supported these findings in a sample of violent prisoners. Similar results of left-approach and right-avoidance motivation were demonstrated in fMRI (Berkman & Lieberman, 2010), PET (Tomer et al., 2008) and transcranial magnetic stimulation studies (TMS) (D'Alfonso et. al, 2000; Hofman & Schutter, 2009). Supporting evidence came from an EEG study by Convit,

Czobor & Volavka (1991) of individuals with antisocial personality disorder. The authors showed a correlation between increased levels of violence and higher left hemispheric activation.

Corpus Callosum

The CC, an important WM bundle, connects the left and the right hemispheres of the brain. Anatomically it is divided from anterior to posterior into the genu, corpus, isthmus and splenium. The anterior part – the genu- connects both PFC's with each other. The CC has a mainly inhibiting role in the submission of information from one side to the other described as transcallosal inhibition (TCI). A very interesting transcranial magnetic stimulation (TMS) study was conducted by Hofman & Schutter (2009). They demonstrated in a healthy population that an aggressive personality style as assessed by the Buss & Perry Aggression Questionnaire (Buss & Perry, 1992) has a direct relationship with a dominant left-sided transcallosal hemispheric inhibition of the right frontal cortex.

WM abnormalities in the CC are commonly found to be linked to aggressive behaviour (see review by Schutter & Harmon-Jones, 2013). In a preliminary study using PET, Raine et al. (1997) reported lower glucose metabolisation in the CC in a population of violent murderers as compared to controls. To assess structural differences in the CC in a group of psychopathic individuals they later conducted a MRI study (2003). Compared to controls Raine et al. found higher WM volumes in the CC in psychopathic individuals, and increased volumes were associated with affective and interpersonal deficits.

In conclusion, the left hemisphere may be related to approach motivation and to generating aggression and anger. The CC may play an inhibiting role involving information transmission between the two hemispheres. More left dominance, by either higher left sided activation or higher left to right inhibition, appears linked to aggression. Remarkably, as I will discuss in the next section, we find structural changes especially in prefrontal WM regions and the CC in MA abuse, which could perhaps explain the higher aggression levels found in individuals with MA abuse (Alicata et al., 2009; Chung et al., 2007; Kim et al., 2009; Oh et al., 2004; Tobias et al., 2010).

PFC

'Frontal lobe syndrome' is a well-known condition, which can result in inappropriate aggressive behaviour (Silver & Yudofsky, 1987). The most famous example of this would be the case of Phineas Cage. In the middle of the 19th century, the railroad worker was injured by an iron rod penetrating his head damaging his complete left frontal lobe (Barker, 1995; Guidotti, 2012). Surprisingly, he did not just survive the injury but was able to walk and speak only minutes later (Harlow, 1848). Although he lived another twelve years, close friends and family members described him as not being himself after the accident. The former hard working and responsible 25-year old became aggressive and could not hold a job (Barker, 1995; Harlow, 1848). Although some of the mental changes have been exaggerated after Phineas' death, it was the first neuroscientific case suggesting behavioural changes out of localized brain damage.

The ventromedial PFC (VMPFC) is situated in the inferior frontal lobe. It plays a role in reward related learning, memory and emotion regulation, especially when behaviour is supposed to change (Rolls, 2004). Therefore, lesions in this part of the PFC have been associated with "disinhibited and social inappropriate behaviour" (Berlin, Rolls & Kischka, 2004). Grafman et al. (1996) studied veterans of the Vietnam War who suffered penetrating injuries to the VMPFC and examined their aggressive behaviour using self-reports and family observations. Higher aggression scores, especially for verbal aggression, were seen in participants with VMPFC lesions compared to controls and patients with lesions in other brain regions.

The right ventrolateral PFC (rVLPFC) plays an important role in "self-control" as Cohen, Berkman & Liebermann (2012) illustrate. They define "self-control" as the ability to inhibit impulses and urges. The activation of the rVLPFC has been correlated in several studies with actively suppressing emotion and the magnitude of activation correlated with the degree of emotional self-control (Cohen, Berkman & Liebermann, 2012). A reduction in VLPFC activation was found in an affect matching task by Payer et al. (2008) in individuals with MA abuse. They argued that diminished socio-emotional integrity could lead to the inappropriate, aggressive behaviour often shown by individuals who abuse MA.

Connection between the PFC and the limbic system

The limbic system is a functional and structural interconnected system with strong connections to the autonomous nervous system and hormone regulation, and serves

important functions in our emotional experience and behaviour. Basic drives like the flight or fight reaction are implemented in this phylogenetically ancient system of the brain. The amygdala as part of the limbic system is mediated by strong connections with the PFC. Lesions in the PFC resulting in less inhibition of the amygdala or lesions in the amygdala itself could be associated with impaired emotion regulation in previous studies (see Review: Seo & Patrick, 2008 or Davidson, Putnam & Larson, 2000; Hoptman, 2003; Payer et al., 2011). The amygdala is important for fear processing. It also plays a role in recognizing angry faces. Adolphs, Tranel & Damasio (1998) asked three patients with complete bilateral amygdala damage to judge faces for trustworthiness and approachability. All three of them judged the most untrustworthy looking faces as very approachable showing that their social judgement is impaired. This misinterpretation of social cues and abnormal fear processing can lead to aggressive behaviour (Hoptman, 2003).

Cingulum

Likewise, the cingulum is found to be associated with aggressive behaviour and drug abuse (Kim et al., 2011; Payer et al., 2011; Sekine et al., 2006). The cingulum contains fibres projecting from the cingulate cortex to the entorhinal cortex. It follows the C shape around the CC from the frontal lobe into the temporal lobe and to the parahippocampal gyrus. The anterior part of the cingulum plays a role in emotion regulation and the posterior part in memory, attention and visual-spatial skills (Aouizerate et al., 2007).

Several studies investigated the relationship of the cingulum and aggression especially in drug abuse. Sekine et al. (2006) showed in a PET study a correlation between 5-HT density and aggression in anterior cingulate areas in individuals with MA abuse. In addition, Payer et al. (2011) found that hyperactivity in the anterior cingulate cortex relates to hostility in MA dependence using fMRI. Kim et al. (2011) focused on the posterior cingulate cortex and parahippocampal gyrus and argued that hyperactivity in these regions could be a cause of “altered emotional experience in social interactions” in their group of individuals with MA abuse.

Furthermore, the cingulum plays a role in drug craving and is part of the reward system of the brain. Wang et al. (2007) found amongst other regions hyperactivation in in the anterior cingulate gyrus in cigarette smokers who experienced cravings after abstinence. In a DTI study, Huang et al. (2013) revealed a negative correlation between the microstructure in the

left anterior cingulum and physical nicotine dependence. In a resting state fMRI study, Janes et al. (2014) found that a rise in nicotine craving was associated with an increase of connectivity in the medial and orbital PFC including the anterior cingulate gyrus.

DTI studies on aggressive behaviour

Next, I will discuss studies investigating aggressive behaviour using DTI. To my best knowledge there is no study yet comparing WM changes detected with DTI and aggressive behaviour in MA dependence. First, there are only a few studies correlating WM integrity directly to aggressive behaviour in other clinical populations or healthy controls. Second, as I will show, several studies investigated WM changes in psychiatric disorders, which are strongly associated with disorders characterized by aggressive and violent behaviour such as conduct disorder, psychopathy, and antisocial personality disorder, although in such work there is no direct correlation with aggression. And third, I will show studies demonstrating an association between WM impairment and impulsivity, given that impulsivity is in turn correlated with aggression (Hoptman et al., 2002).

All but one study of Beyer et al. (2014) found a correlation between decreased WM integrity and increased aggressive behaviour. Hoptman et al. (2002) demonstrated in their DTI study of individuals with schizophrenia a correlation between lower FA values in the right inferior frontal WM and aggression scores on a self-report questionnaire. Similar associations between anger and hostility and inferior frontal WM changes were found by Ruesch et al. (2007) in women with borderline personality disorder and comorbid attention deficit hyperactivity disorder. They observed increased MD in the right inferior frontal WM, which correlated positively to self-report measures of anger and hostility.

Peper et al. (2014) studied WM integrity in a group of healthy adolescents and found a correlation between higher scores on the Buss & Perry Aggression Questionnaire and decreased FA, increased RD (radial diffusivity), LD (longitudinal diffusivity) and MD in the fronto-temporal-subcortical network. A study conducted by Saxena et al. (2012), investigating aggression in bipolar disorder, found a negative correlation between lower FA values in the anterior commissure and genu of the CC, and aggressive behaviour. The correlation between values in the CC genu however, did not survive correction for multiple comparisons.

There is one study examining WM integrity in the uncinate fascicle and trait aggression in healthy adults using DTI. Since the inhibitory control of the OFC over the amygdala is relevant for emotion regulation it was assumed that disruptions in that connection could play a role in aggression. Beyer et al. (2014) found no relationship between trait aggression and the connectivity between the OFC and amygdala (= uncinate fascicle). The authors argue that perhaps fronto-limbic disconnectivity can only be shown in pathologic aggression as shown in studies below.

It is well established, then, that WM impairment plays a role in psychiatric disorders, which are characterized by displaying patterns of aggressive behaviour and emotion regulation deficits. As discussed above, the following studies did not specifically correlate imaging findings with aggression, but aggressive behaviour plays a major role in these disorders.

Passamonti et al. (2012) found changes in the anatomical connection between the OFC and the amygdala in participants with conduct disorder. FA values were *increased* in the uncinated fascicle compared to healthy controls. Results by Craig et al. (2009) on the other hand showed *reduced* FA in the right uncinate fascicle but not in the left in psychopathy. The authors found a trend towards a negative correlation of behavioural scores and FA values in the right uncinate fasciculus. Using voxel-based analyses Sundram et al. (2012) found even broader changes throughout the brain in a sample of participants with antisocial personality disorder. The authors found, consistent with Craig et al. (2009), reduced FA in the right uncinate fascicle. Furthermore, they showed reduced FA bilaterally in the genu of the CC, the right anterior corona radiata and right anterior limb and genu of the internal capsule and the right inferior fronto-occipital fasciculus. The FA values in the frontal lobes of individuals with antisocial personality disorder also correlated negatively to antisocial behavioural scores. Again consistent with Craig et al. (2009), reduced FA in the genu of the CC was found by Sundram et al. (2012) in their sample of adults with antisocial personality disorder and these FA changes correlated negatively with psychopathy scores.

One very recent study from Zhang et al. (2014) revealed that impulsivity was associated positively with increased FA values in the genu and body of the CC and the right superior corona radiata in a group of adolescent with conduct disorder. On the other hand, Moeller et al. (2005) found a negative correlation between FA values in the anterior CC and impulsivity in individuals with cocaine dependence. Higher FA values in the group of

adolescent participants of Zhang et al. could be due to reactive gliosis and different maturation in the adolescent brain. This is supported by findings from a study by Colby et al. (2012) who similarly found increased FA values in children with prenatal MA exposure in the anterior corona radiate and genu of the CC. The authors argue that higher FA values could be due to compensatory mechanisms because of MA damages to the developing brain.

Taken together, WM changes in frontal brain areas seem to exist across diagnoses in samples of psychiatric disorders characterized by increased aggressive behaviour.

1.4 Hypothesis and Objectives

Several neuroimaging studies showed dysregulation of frontal lobe function or frontal structural changes in impulsive and violent behaviours. Reduced regulation of the frontal cortex over subcortical structures might be a risk factor for development of aggression. The altered connectivity between frontal and subcortical especially limbic regions might be due to WM impairment.

Based on the literature review, the aim of this study was to delineate possible relationships between WM changes and aggression in MA dependence. I therefore compared WM integrity of abstinent individuals with MA dependence with a group of healthy control subjects using DTI. As a measurement of aggressive behaviour, I used the self-report Buss & Perry Questionnaire. The resulting aggression scores were then correlated with WM impairment to assess a possible association between the two.

The hypotheses were that:

1. The MA group would show lower FA and $\lambda_{\parallel}$ values, as well as higher MD and $\lambda_{\perp}$ values compared to healthy controls, reflecting structural WM changes in the former group.
2. Buss & Perry Questionnaire self-report scores would be higher in individuals with MA dependence than in healthy controls.
3. WM damage, especially in frontal lobe areas, would be significantly associated with aggressive behaviour in individuals with MA dependence.

To investigate WM changes in the two study groups, I chose both a theory-based region of interest (ROI) and an explorative whole-brain analytic approach. As an explorative method, I compared the MA group and the healthy controls in a tract-based spatial statistical (TBSS) analysis as explained in the Methods chapter.

As previous research shows, WM changes in MA abuse as well as in aggressive behaviour are commonly found in frontal areas. For the ROI analysis, I therefore chose to investigate WM tracts in the frontal areas of the left and right hemisphere respectively. Based on the John Hopkins University (JHU) ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008), I included the following WM tracts:

(1) the genu of the Corpus Callosum (CC)

The left and the right side of the brain are connected by a WM bundle called the CC. Anatomically it is divided from anterior to posterior into the genu, corpus, isthmus and splenium. The CC, especially the genu as a connection of the prefrontal cortices of the hemispheres, plays an important role in regulating emotions (Nowicka & Tacikowski, 2011; Schutter & Harmon-Jones, 2013).

(2) the cingulum (CgG; CgH)

The cingulum forms the WM core of the cingulate gyrus. It is an association bundle with long and short fibres carrying information from the cingulate gyrus to the hippocampus. It also links the prefrontal and the parahippocampal cortices (Goldman-Rakic, Selemon & Schwartz, 1984). The JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) divides the cingulum into two parts - the cingulum in the cingulate gyrus (CgC) and in the hippocampal region (CgH). They are divided at the axial level of the splenium of the CC.

(3) the uncinate fasciculus

The uncinate fasciculus connects the orbito-frontal lobe with the hippocampus and amygdala in the anterior temporal lobe. This tract is considered part of the limbic system and WM changes are commonly found to be associated to aggressive behaviour as discussed above.

In the next chapter, I am going to explain the recruitment process as well as questionnaires and statistical procedures used in this research. It also contains an introduction to DTI analysis using FSL.

2. Methods

2.1 Recruitment

Recruitment of participants with MA dependence was undertaken in a number of drug counselling and rehabilitation facilities in the greater Cape Town area. Healthy control subjects were recruited from the same communities as the individuals with MA dependence, through word of mouth and by means of flyers to match them as close as possible in terms of gender, age, years of education, ethnicity and social circumstances. All participants were right handed, fluent in English and between 18 and 40 years of age. Inclusion criteria for the MA group were 1) diagnosis of MA dependence on the Structured Clinical Interview of DSM IV Disorders (SCID-I), and 2) current drug abstinence. Exclusion criteria for all participants were 1) substance dependence (except nicotine for all participants and except MA for the MA group) 2) current or a history of a psychiatric disorder 3) severe medical or neurological illness or trauma including head injuries, and 4) a history of seropositive testing for HIV (HIV status was not tested in the study out of ethical reasons). Additionally, participants with conditions which would prohibit MRI scanning like 5) metal implantation or 6) claustrophobia were excluded. Until 2014, the umbrella study screened 174 participants, of which 83 had to be excluded due to ineligibility, 6 participants withdrew their consent, and 15 participants were lost in the follow up process. During my affiliation with the study in 2014, 26 participants were screened, of which 5 did not meet our inclusion criteria and were excluded. In total, we found 91 participants to be eligible. 11 scans were excluded due to quality issues (head movement, distortion etc.). Finally, we included scans in the data analysis of 40 participants with MA dependence and 40 matched healthy controls.

This fairly matched our beforehand determined sample size of 84 participants. Following output parameters were acquired using power calculations for two tailed t-test in GPower analysis software (input parameters: Alpha= 0.05; 1-ß = 0.95; Effect size d= 0.8 (large effect); Allocation ratio N2/N1: 1):

Critical t: 1.9893186

Total sample size: 84

Actual power 0.9518269.

Participants received supermarket food vouchers for the interview and the brain scan as compensation for food and travel expenses. Before individuals entered the study informed consent was obtained in writing, after insuring that the participant fully understood the study methods and had time to ask questions.

SCID

To determine eligibility for participation according to the study's inclusion and exclusion criteria all participants underwent a clinical assessment. This was carried out by a trained clinician in the Department of Psychiatry and Mental Health using the Structured Clinical Interview for DSM-IV Disorders Researchers version (SCID-I for DSM-IV-TR) (First et al., 2002). The SCID is a semi-structured interview, which focuses on diagnosing Axis I disorders. The language of the SCID is intended to be understood by individuals with a grade 8 level of education or higher. Even though it was not an exclusion criterion, all of the participants completed at least grade seven.

We included the following modules:

A. Mood Episodes
B. Psychotic and Associated Symptoms
C. Psychotic Disorders
D. Mood Disorders
E. Substance Abuse
F. Anxiety Disorders
G. Somatoform Disorders
H. Eating Disorders

Demographic details, including ethnicity, language, employment status, and number of years of schooling completed, were documented. Additionally, we kept a record of drug use measures, together with life-time use of all major drug types, MA use onset, duration of MA use, and duration of MA abstinence.

2.2 Behavioural Measures

A questionnaire by Buss & Perry (1992) designed to assess aggressive behaviour was given to the individuals with MA dependence and healthy control participants. The questionnaire measures four dimensions of aggression: Physical Aggression, Verbal Aggression, Anger, and Hostility. These are assessed by 29 statements the participant has to rank as "extremely uncharacteristic of me" to "extremely characteristic of me" on a 5-point scale. Questions for Physical Aggression include e.g., "*I have become so mad that I have broken things*"; Verbal Aggression "*When people annoy me, I may tell them what I think of them*"; Anger "*Some of*

my friends think I am a hothead" and Hostility "*I am suspicious of overly friendly strangers*". The subscales Physical Aggression with 9 items and Verbal Aggression with 5 items represent the "disinhibited" behavioural aspects, Anger including 7 items the affective and Hostility with 8 items the "inhibited" cognitive aspect of aggression (Anderson & Bushman, 2002). Scores range from 29 points to a maximum score of 145 points. Lower scores indicate a lower aggression level and higher scores more aggressive behaviour.

The questionnaire is widely used and reliability and validity have been demonstrated repeatedly (Bernstein & Gesn, 1997; Harris, 1997; O'Conner, Archer &Wu, 2001; Tremblay & Evart, 2005). Although some researchers recommend removing some items of the questionnaire (Harris, 1995; Vigil-Colet et al., 2005), the psychometric properties are sound. There have also been a few studies, which tested the generalizability of the questionnaire internationally with reassuring results (Fossati et al., 2003; Gerevich, Bácsakai & Czobor, 2007; Nakano, 2001; von Collani & Werner, 2005). On the other hand, Becker (2006) states that influences of social desirability when answering the questions are a weakness of the test. Then again, Darke et al. (1998) have shown that the self-report measures in substance abuse participants tend to be accurate "when compared to biomarkers, criminal records and collateral interviews".

2.3 DTI analysis

Brain imaging sequences

Brain imaging was conducted using a 3T Siemens Magnetom Allegra at the Cape Universities Brain Imaging Centre (www.sun.ac.za/cubic). Full-brain DTI images were acquired with the following sequence: orientation=transversal; slices=70; distance factor=0; voxel size=2x2x2 mm^3; TR=9500ms; TE=88ms; diffusion directions=30; b-value=1000s/mm^2; 4 reference b0 scans; 120x120 matrix; FOV=240mm; FOV phase=100%; scan time=5:33minutes, repeated three times.

Scans were checked for structural abnormalities for both groups by a study independent radiologist. To control for acute drug use a five panel urine screen was performed before the scan testing for MA, amphetamines, opioids (morphine), Tetrahydrocannabinol (THC) and cocaine (Acon® 5-panel urine test).

Data analysis

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain software library (FSL) (Smith et al., 2004) was used for analysing the DTI data.

Fractional anisotropy (FA), a measure of the directionality of water diffusion in WM fibres, mean diffusivity (MD), a direction-independent measure of local water diffusion, and the eigenvalues (λ1, λ2, λ3) were calculated. From the eigenvalues, the perpendicular Diffusivity ($\lambda_\perp$) was determined, being the mean of the two perpendicular eigenvalues λ2 and λ3, as well as the parallel Diffusivity ($\lambda_\parallel$), being λ1. These measures were subsequently put into FSL's Tract Based Spatial Statistics (TBSS) tool (Smith et al., 2006), which uses robust methods of quantifying localised WM differences between study groups.

To prepare the data for use in FSL, DICOM images were converted to NIfTI format using the program Mcverter in Matlab. An in-house script was used following the pre-processing steps of TBSS. This script embodied FSL analysis tools, specifically Eddy correction, Brain Extraction (BET) and DTIfit as explained below (Smith et al., 2004). Eddy correction was used to correct for head movement and distortion caused by eddy currents of the gradient coils of the MRI machine. For creating a brain mask and for removing skull and meninges from our data, images in a second step got brain-extracted using BET [Brain Extraction Tool] at the recommended threshold of 0.3. The script continues with fitting a tensor model to each voxel of the data using DTIfit within the FDT toolbox [Functional MRI of the Brain Diffusion Toolbox] providing us with the following output:

V1 - 1st eigenvector

V2 - 2nd eigenvector

V3 - 3rd eigenvector

λ1 - 1st eigenvalue

λ2 - 2nd eigenvalue

λ3 - 3rd eigenvalue

$\lambda_\perp$ - perpendicular diffusivity

MD - mean diffusivity

FA - fractional anisotropy

S0 - raw T2 signal with no diffusion weighting

After pre-processing was completed, a visual quality check for warping and segmentation defaults was performed.

Two different approaches of comparison of WM differences between the two groups were carried out; an explorative whole-brain voxel wise analysis and a theory based ROI method. ROI analysis was performed at three prefrontal regions defined by the JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008).

I chose TBSS within FSL as an analytic tool, because it resolves potential alignment and smoothing issues encountered with other analysing methods, like voxel-based morphometry (VBM), in two steps. First, approximate nonlinear registration is performed as described below. Following, a skeleton of all WM tracts common to the study group is generated and each subject's DTI measures are then projected onto the skeleton so that each skeleton voxel takes the value from the centre of the nearest tract.
However, since DTI relies on the microstructural architecture of WM, in areas with crossing fibres, TBSS is still problematic and results have to be interpreted carefully.

TBSS

For voxel wise statistical analysis I used following codes as provided within TBSS (Smith et al., 2006).

tbss_1_prepoc *.nii.gz

The first preprocessing step in TBSS abrades the images and zeros the end slides.

tbss_2_reg -T

Then, all FA images were aligned into 1×1×1mm^3 Montreal Neurological Institute- 152 (MNI152) common space using the nonlinear registration tool FNIRT within FSL. The –T option in the code uses the FSL standard template FMRIB58_FA as registration surface for all subjects FA images (Jenkinson & Smith, 2001).

tbss_3_postreg -S

Following, a mean FA image, from all the subjects FA images combined, was created. To check for effective registration the mean FA image was inspected following all major WM tracts. Next, the mean FA image was thinned and skeletonized resulting in a m*ean_FA_skeleton* image, which represents the centres of all tracts common to all subjects. To confirm good

alignment results, every single FA image (*all_FA*) was loaded onto the *mean_FA_skeleton* for quality control using FSLview.

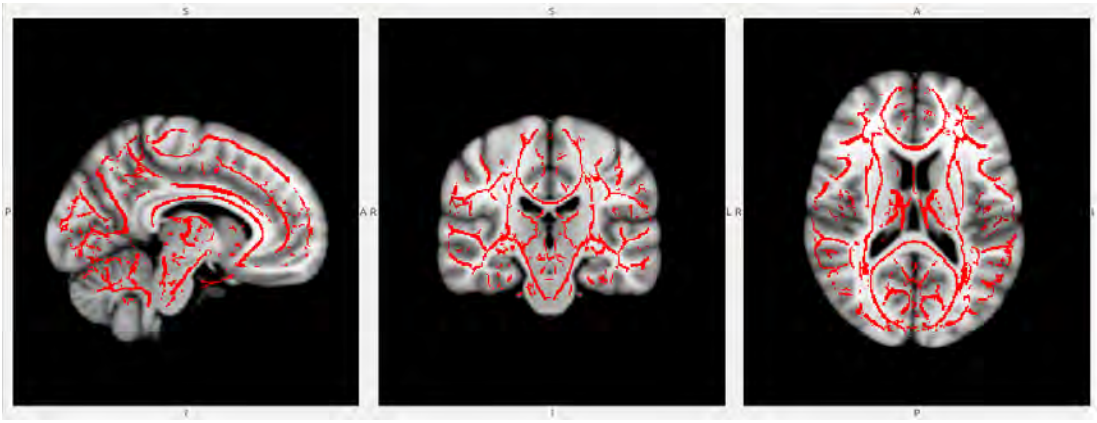

Figure 1: mean_FA_skeleton. This shows the major WM tracts of all subjects of both groups.

tbss_4_prestats 0.2

In the last step, the threshold for FA values was set at 0.2 to ensure that only voxels within WM were used in the next projection step (Smith et al., 2006). Now each single FA image was projected onto the *mean_FA_skeleton* by choosing the FA value closest to the tract centre. As an outcome, I got a 4D image file with all the projected skeletonised FA data called *all_FA_skeletonised* with the fourth dimension being the subjects. This file was used in voxel-wise cross-subject statistics for further analysis.

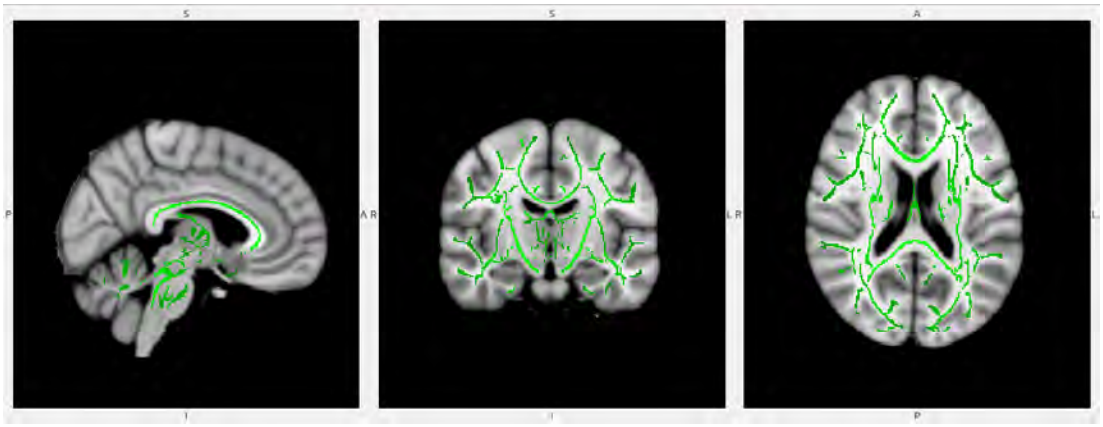

Figure 2: all_FA_skeletonised. This shows an image of one subject's skeletonised FA map.

For processing of non FA images including MD, $\lambda_{\parallel}$ and $\lambda_{\perp}$ in TBSS, I used the following command:

tbss_non_FA

This script combines all steps within TBSS above and uses the mean_FA_skeleton as a projection for the all_non_FA image files resulting in an all_non_FA_skeletonised image for each measure subsequently.

Randomise

I used Randomise version 2.0 from the FSL toolbox for voxel-wise permutation-based nonparametric analysis (Nichols and Holmes, 2002) on the skeletonized FA, MD, $\lambda_{\parallel}$ and $\lambda_{\perp}$ data to identify WM differences between our two study groups. Design matrix and design contrast (Control > MA; MA > Control) files were created using the General linear model setup (Glm GUI) with study group as independent variable and age and gender as covariates. I used 5000 random permutations as recommended by the FSL user guide to test our contrasts at a significance level of $p < 0.05$. Multiple comparisons correction using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) was performed with a cluster-wise significance level at $p < 0.05$.

The outcome was a set of files containing raw *t*-test statistic images (unthresholded) and TFCE p-value images fully corrected for multiple comparisons across space. I then masked our raw *t*-test statistic images with significant voxels of the fully corrected images (corrp) respectively using fslmaths from the toolbox on a threshold of 1-p (0.95).

fslmaths MA_output_tfce_corrp_tstat1 -thr 0.95 -bin -mul MA_output _tstat1 MA_output _thresh_tstat1

The above command resulted in two threshold *t*-test statistic images, which then could be used to extract clusters across the brain.

The last step provides us with a table containing information about the cluster index, number of voxels in one cluster, maximum voxel intensity and location in MNI space. These coordinates could then be used to localize WM changes using the JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008).

cluster --in= Meth_output _thresh_tstat1 --thresh=0.05 --oindex= Meth_output _cluster_index --olmax=grot_lmax.txt --osize= Meth_output _cluster_size

For visualizing the results, FSLview was used by overlaying the resulting clusters over a standard brain template (MNI152_T1_1mm_brain).

Region of Interest analysis

In the second approach to delineate WM differences between the two groups, I used a ROI method. ROI masks for the three frontal predefined WM regions labelled by the JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) were created using an in-house script. FA, MD, $\lambda_{\parallel}$ and $\lambda_{\perp}$ values were extracted from following regions for the left (LH) and right (RH) hemisphere respectively:

(1) the genu of the CC,

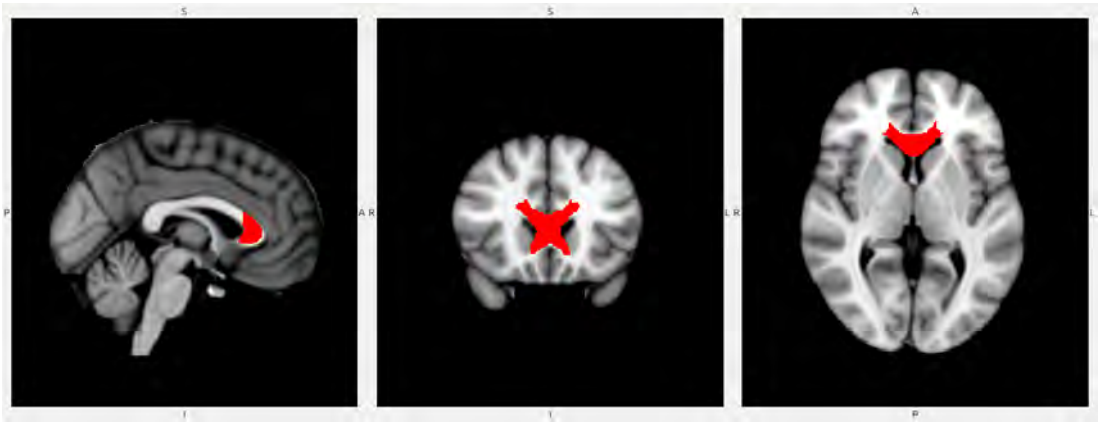

Figure 3: Region of Interest mask for the genu of the corpus callosum.

(2) the cingulum,

(2.1) cingulate gyrus section (CgC),

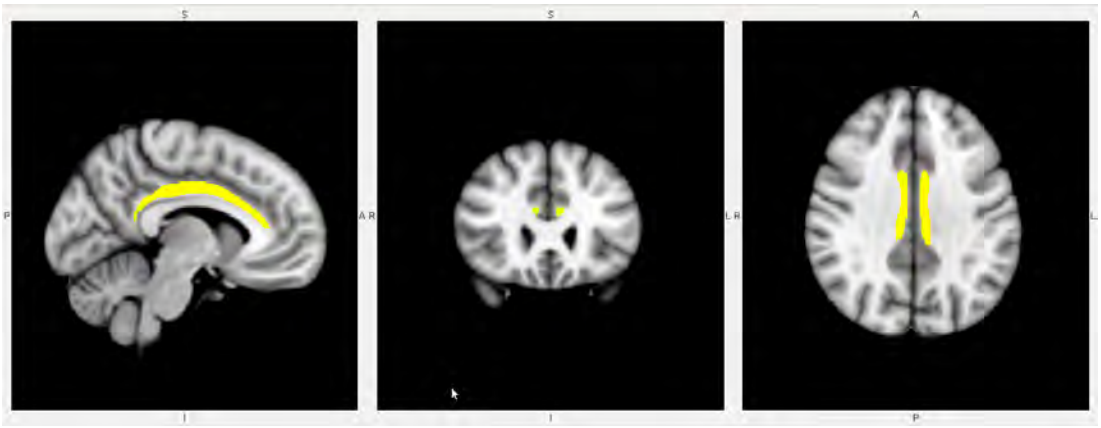

Figure 4: Region of Interest mask for the cingulate gyrus section of the cingulum.

(2.2) hippocampal section (CgH),

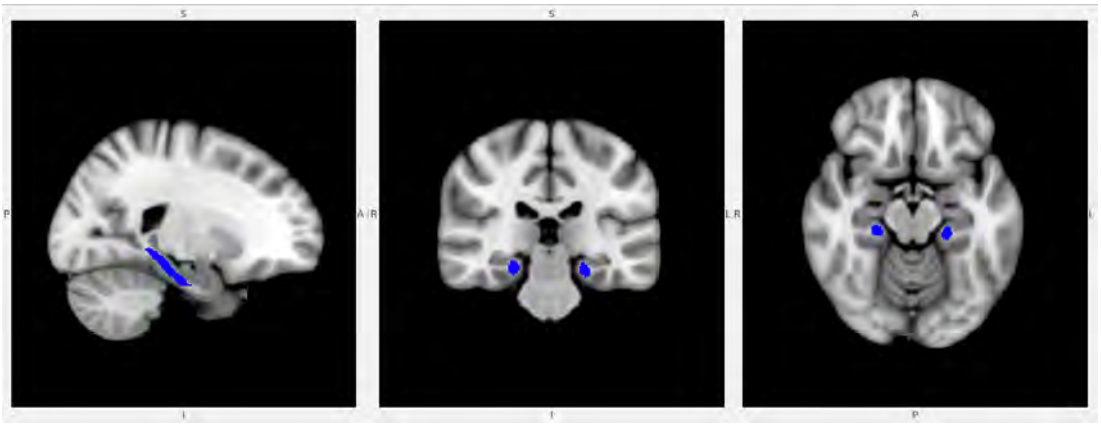

Figure 5: Region of Interest mask for the hippocampal section of the cingulum.

(3) and the uncinate fasciculus.

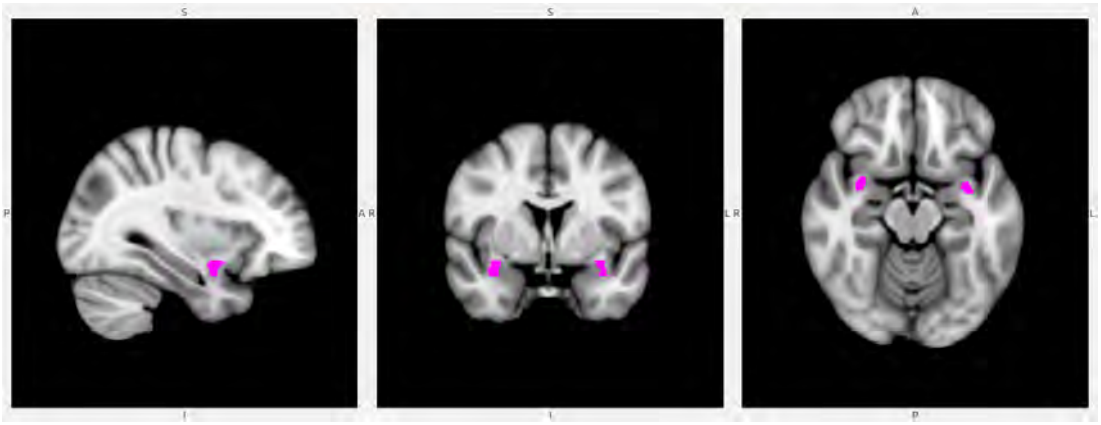

Figure 6: Region of Interest mask for the uncinate fasciculus.

The advantage of this computed form of ROI extraction is that there is no arbitrary drawing of ROI seeds, which could influence the results. The script compiles a table with all subjects measured values for FA, MD, $\lambda_{\parallel}$ and $\lambda_{\perp}$ for each region of interest respectively. This table was subsequently put into SPSS for statistical analysis.

2.4 Statistical analysis

All statistical analyses were done in SPSS (version 22). All data was tested for normal distribution using the Shapiro Wilk test. Group comparison of demographic data was done using the Mann-Whitney-U test for non-parametric data and Pearson Chi-square test for parametric categorical data. Multivariate analysis of variance (MANOVA) was done for the

Buss & Perry Questionnaire with total score and subscales as 'dependent factors' and study groups as 'fixed factor'. Given a significant overall test, individual questionnaire scores were compared between groups using independent 2-sample *t*-test. DTI measures were analysed with Mann-Whitney-U test for non-parametric data. Spearman correlation was used to investigate the relationship of aggression scores and WM differences as well as MA use measures (onset of use, duration of use and abstinence) and WM differences. To correct for multiple comparison, I used the 2-staged linear step up procedure of the false discovery rate control (FDR) (Benjamini, Krieger and Yekutieli, 2006) for each WM structure. The criterion for statistical significance for all tests was at $p < 0.05$ (2-tailed).

2.5 Ethics statement

The study was conducted in accordance with the guidelines of The Declaration of Helsinki (Edinburgh 2000) and approved by the Human Ethics Research Committee of the Faculty of Health Sciences at the University of Cape Town University (HREC 395/2014). The study is part of an ongoing methamphetamine umbrella study (HREC 340/2009).

Before entering the study, participants gave informed consent by signing a consent form. The study was explained to every participant and it was made clear that the study was entirely voluntary and that they could withdraw their consent at any time during their participation. It was also explained that all information was kept confidential, ensuring that we used study codes instead of names for further processing. The study did not entail significant direct risk or harm to the participants.

3. Results

3.1 Participants

Table 1 presents demographic data of the MA and control group. Participants did not differ significantly in gender, age, alcohol or cannabis consumption. However, the MA group had less years of education (p= 0.001) and more tobacco (p=0.007) and methaqualone (p=0.026) consumption then the control group. Individuals with MA dependence were in median 21 days abstinent. The median duration of MA use was 6.5 years and the median age MA abuse was started was 17 years old.

Table 1: Demographic and methamphetamine use measures

DEMOGRAPHIC MEASURES	**MA N=40**	**CTRL N=40**	**TEST FOR GROUP DIFFERENCE**
MALE/FEMALE, N	29/11	29/11	$\chi^2(1)=.000$, $p=1.0$
AGE IN YEARS, MEDIAN (RANGE)	25.5 (18-38)	25 (18-38)	$U=762.5$, $p=.721$
LEVEL OF EDUCATION IN YEARS, MEDIAN (RANGE)	10 (8-15)	12 (9-14)	***U*=481.0, *p*=.001***
TOBACCO SMOKERS, N	34	22	**$\chi^2(1)=8.571$, $p=.007$***
ALCOHOL CONSUMERS, N	21	17	$\chi^2(1)=0.802$, $p=.502$
CANNABIS USERS, N	9	14	$\chi^2(1)=1.526$, $p=.323$
METHAQUALONE USERS, N	5	0	**$\chi^2(1)=5.475$, $p=.026$***
MA USE MEASURES			
AGE OF ONSET IN YEARS, MEDIAN (RANGE)	17 (12-32)		
DURATION IN YEARS, MEDIAN (RANGE)	6.5 (2-19)		
ABSTINENCE IN DAYS, MEDIAN (RANGE)	21 (1-240)		

**significant differences between Groups; MA= methamphetamine group; CTRL= control group; N= numbers*

3.2 Behavioural Measure

Four participants in the control group did not complete the Buss & Perry Questionnaire. Multivariate analyses showed a significant difference between groups (p<0.001) so that independent t-tests were used for individual group comparisons. Mean aggression scores for Anger (p<0.001), Physical Aggression (p=0.032) and Total score (p=0.021) were significantly higher in the MA group then in the control group. However, Anger showed a medium effect size (d= 0.41) and Physical Aggression (d=0.25) and Total scores (d=0.26) a low effect size. All group differences survived FDR correction. Study groups showed no differences in Hostility or Verbal Aggression scores. Despite the fact that these are ordinal data, we conducted an

analysis of covariance (ANCOVA) test to estimate the effects of education on aggression scores; Pillai's trace test showed no statistically significant effect for any of the subscales ($F(5,69)=0.698$, $p=0.627$).

Table 2: Buss & Perry Questionnaire scores

BUSS &PERRY QUESTIONNAIRE	MA N=40	CTRL N=36	GROUP DIFFERENCE	EFFECT SIZE
PHYSICAL AGGRESSION	26.63 ± 8.625	22.58 ± 7.36	***t*(74)= 2.19, *p*= .032***	***d*= 0.25**
VERBAL AGGRESSION	16.30 ± 4.23	15.72 ± 3.44	*t*(74)= 0.65, *p*= .519	*d*=0.08
ANGER	20.88 ± 5.8	16.11 ± 4.73	***t*(74)= 3.90, *p*< .001***	***d*=0.41**
HOSTILITY	24.68 ± 7.18	22.14 ± 7.89	*t*(74)= 1.47, *p*= .147	*d*=0.17
TOTAL	88.48 ± 23.54	76.44 ± 20.75	***t*(74)= 2.35, *p*= .021***	***d*=0.26**

Scores in Mean ± Standard Deviation, MA= methamphetamine group, CTRL= control group, N=number

3.3 DTI analysis

TBSS analysis within FSL

Between-group voxel wise whole-brain comparison revealed higher MD values in the right superior corona radiata in the MA group, compared to healthy controls. The cluster containing 250 voxels was found in the right superior corona radiata at x/y/z = 18/-22/55. Significance levels within Randomize were set at $p<0.05$ and results were corrected for multiple comparisons within the program.

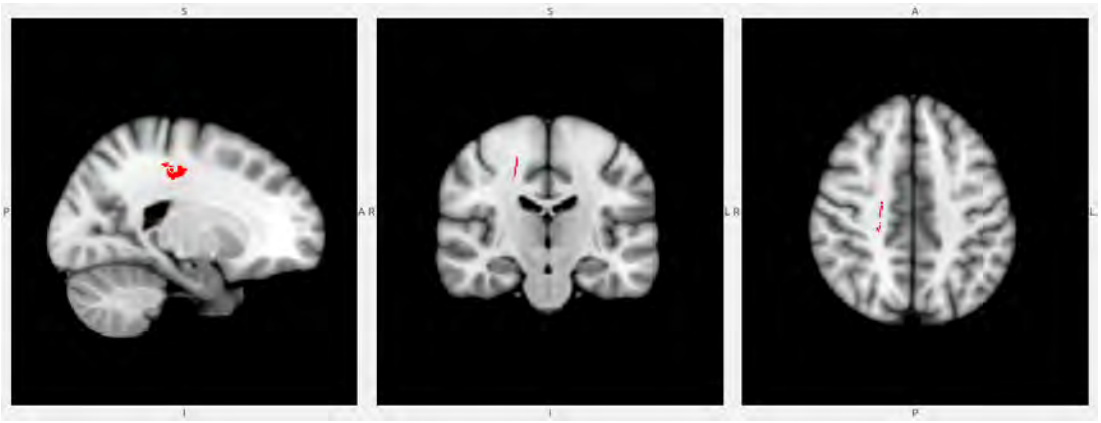

Figure 7: Results: TBSS analysis. Increased mean diffusivity values in the right superior corona radiata in the methamphetamine group.

Region of Interest analysis

Table 3 shows the median FA, MD, $\lambda_{\perp}$ and $\lambda_{\parallel}$ values for the three WM regions of interest. I found significantly lower FA values in the left cingulum (CgC) (*U*=545.0, *p*=0.014, *d*= -0.27) of individuals with MA dependence but not in the right CgC. FA values in the left CgC did not survive FDR correction. I also found significantly higher MD values in MA users compared to healthy controls bilateral in the hippocampal region of the cingulum (RH: *U*=541.5, *p*=0.012, *d*=- -0.28; LH: *U*=550.5, *p*=0.016, *d*= -0.27), but only the effects in the RH survived FDR correction. MD (*U*=439.5, *p*=0.001, *d*= -0.39) and $\lambda_{\perp}$ (*U*=561.5, *p*=0.021, *d*= -0.26) values in the genu of the CC were higher in the MA group than in controls and both effects survived FDR correction. There was no difference in the uncinate fasciculus between the two groups. There were also no differences in $\lambda_{\parallel}$ values between the two groups.

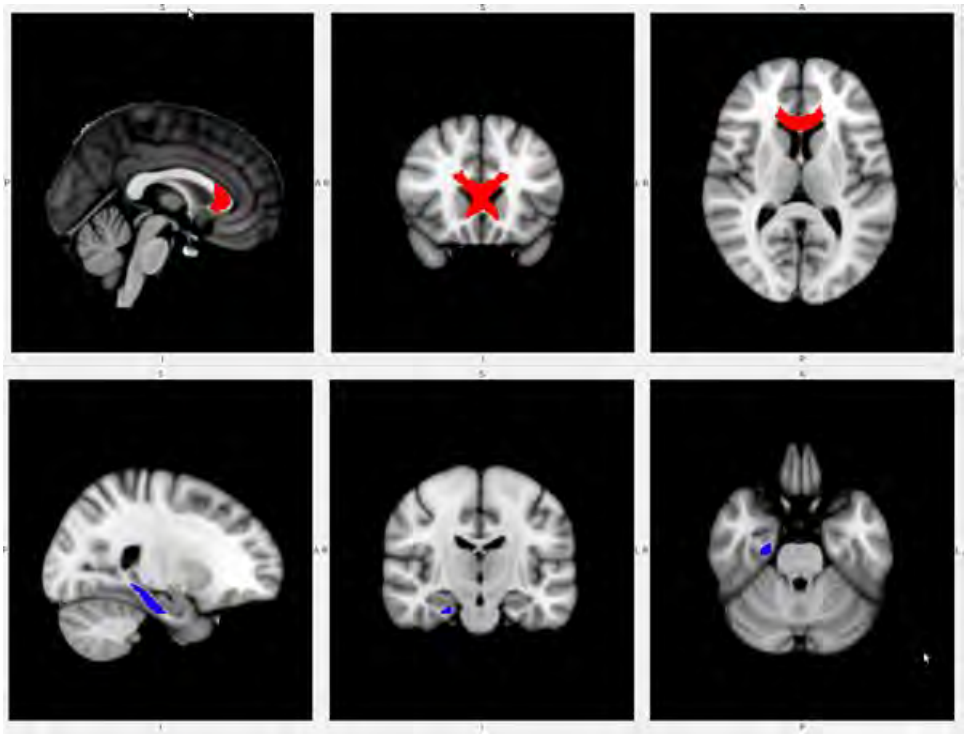

Figure 8: Results: Regions of Interests analysis showing significant results. Red: Increased mean diffusivity and perpendicular diffusivity in the genu of the corpus callosum in the methamphetamine group. *Blue*: Increased mean diffusivity in the right hippocampal area of the cingulum in the methamphetamine group.

Table 3: Mean values of DTI measures in predefined Regions of Interest

REGION OF INTEREST	DTI MEASURE	MA MEDIAN (RANGE)	CTRL MEDIAN (RANGE)
CORPUS CALLOSUM GENU	FA	.441 (.331-.495)	.451 (.322-.513)
	MD**	.0007865 (.000753-.000897)	.0007715 (.000659-.000849)
	$\lambda_{\perp}$**	.0005785 (.000536-.000728)	.00057 (.000481-.000675)
	$\lambda_{\parallel}$	.001199 (.001107-.001336)	.0011895 (.001014-.001259)
CINGULUM RH	FA	.414 (.304-.473)	.429 (.366-.492)
	MD	.000731 (.000709-.000777)	.000729 (.00069-.000786)
	$\lambda_{\perp}$	.000558 (.000516-.000609)	.0005485 (.000501-.000607)
	$\lambda_{\parallel}$	.0010855 (.000939-.001158)	.0011 (.001002-.001166)
CINGULUM LH	FA*	.407 (.307-.461)	0.423(.359-.478)
	MD	.0007295 (.0007295-.000784)	.000728 (.000682-.000795)
	$\lambda_{\perp}$	.000559 (.000518-.000616)	.0005505 (.000499-.000615)
	$\lambda_{\parallel}$	.0010815 (.00093-.001144)	.001093 (.00098-.001156)
CINGULUM HIPPOCAMPUS RH	FA	.447 (.325-.510)	.448 (.370-.520)
	MD**	.0006995 (.000657-.000737)	.0006825 (.000655-.000786)
	$\lambda_{\perp}$	.00051 (.000456-.000588)	.000501 (.000459-.000589)
	$\lambda_{\parallel}$	.0010705 (.000982-.001145)	.0010515 (.000957-.001181)
CINGULUM HIPPOCAMPUS LH	FA	.431 (.294-.505)	.441 (.316-.514)
	MD*	.000701 (.000644-.00082)	.000684 (.000649-.000831)
	$\lambda_{\perp}$	.000522 (.000476-.000642)	.00051 (.000463-.000654)
	$\lambda_{\parallel}$	.001038 (.000925-.001176)	.0010405 (.000944-.001184)
UNCINATE FASCICULUS RH	FA	.373 (.230-.436)	.389 (.223-.477)
	MD	.0015005 (.001237-.002006)	.001489 (.001176-.002322)
	$\lambda_{\perp}$	.001203 (.000937-.001818)	.0012035 (.000885-.0021)
	$\lambda_{\parallel}$	.0021125 (.001708-.002382)	.0020995 (.001698-.002766)
UNCINATE FASCICULUS LH	FA	.468 (.326-.540)	.467 (.360-.536)
	MD	.000767 (.000719-.00097)	.0007575 (.00067-.000919)
	$\lambda_{\perp}$	.0005575 (.000505-.000803)	.000563 (.000447-.000735)
	$\lambda_{\parallel}$	.0011785 (.00106-.001368)	.0011665 (.001081-.001286)

***** = group difference did not survive FDR correction **= group difference survived FDR correction*
FA= fractional anisotropy; MD= mean diffusivity; $\lambda_{\perp}$= perpendicular diffusivity; $\lambda_{\parallel}$= parallel diffusivity
CTRL= control group; MA= methamphetamine group; RH= right hemisphere; LH= left hemisphere

Correlational analysis

Spearman correlational analysis showed a negative correlation between MD in the genu of the CC and total aggression score (*r*= -.315, *p*=0.047) in MA users but the effects did not survive FDR correction. Additionally, $\lambda\perp$ values in the CC genu inversely correlated with Physical Aggression (*r*= -.366, *p*= 0.02) and Total score (*r*= -.380, *p*= 0.016) in the MA group, but likewise, these effects did not survive FDR correction.

The MD values in the superior corona radiata did not correlate with aggression scores. There was no correlation between DTI measures and MA use, i.e. duration, abstinence, or age started. Also, no correlation was found between WM integrity and aggression scores in the control group.

Table 4: Correlational analysis between corpus callosum and aggression

BUSS & PERRY QUESTIONNAIRE	**CORPUS CALLOSUM GENU**	
	MD	$\Lambda\perp$
PHYSICAL AGGRESSION	*r*= -.217, *p*=.178	***r*= -.366, *p*= .02***
ANGER	*r*= -.226, *p*=.162	*r*= -.286, *p*=.073
TOTAL	***r*= -.315, *p*=.047***	***r*= -.380, *p*=.016***

***** = did not survive FDR correction, *p*= *p*(2-tailed); MD= mean diffusivity; $\lambda\perp$= perpendicular diffusivity

4. Discussion

The aim of this study was to delineate the relationship of aggressive behaviour and WM structural changes in MA dependence using DTI.

There were three main findings. In line with our first hypothesis, the study showed WM changes in individuals with MA dependence compared to controls. A TBSS analysis revealed increased MD values in the right superior corona radiata in the MA group. Furthermore, using ROI analysis, I found increased MD and $\lambda_{\perp}$ values in the genu of the CC in individuals with MA dependence. MD values were also increased in the MA group in the right hippocampal region of the cingulum. Additionally, in line with the second hypothesis, individuals with MA dependence showed higher scores of aggression on the Buss & Perry Questionnaire, particularly in the subscales of Anger and Physical Aggression. Third, contrary to expectation, I did not find a significant correlation of WM changes with aggressive behaviour.

WM changes

Our finding of increased MD values in the right corona radiata is consistent with several previous publications. Tobias et al. (2010) found decreased FA values in the right superior corona radiata in individuals with MA dependence. Moreover, impaired WM integrity in the superior corona radiata was shown in several studies in cocaine dependent individuals (Bell et al., 2011; Lane et al., 2010) and other substance dependences (Jacobus et al., 2013; Qiu et al., 2014). Changes in WM structure in the right superior corona radiata, an association fibre bundle connecting cortico-limbic structures, have been linked to increased risk taking behaviour, and decreased impulse control (Berns, Moore & Capra, 2009; Jacobus et al., 2013; Qiu et al., 2014). Unlike Tobias et al. (2010), we did not detect any changes in FA but MD. Next, I am going to give possible explanations for that difference.

Controversy exists regarding changes in DTI measures and their structural foundation on a neuronal level. However, the observed increase of MD values in our study might be due to a decrease in membrane density due to cell degeneration (Beaulieu, 2002; Douaud et al., 2011). Decreases in FA and increases in MD can happen independently. Changes of FA values rely on coherent fibre orientation and it has been shown that in areas of crossing fibres FA values might not change (Douaud et al., 2011; Pierpaoli et al., 2001). Furthermore, a loss in WM fibres does not affectedly reduce diffusion anisotropy (Pierpaoli et al., 2001). Moreover, a loss of complexity of WM fibre orientation can increase FA values rather than diminish them

(Hoare et al., 2010; Stebbins et al., 2007). This might be an explanation of why we did not find FA changes in our data.

Additionally, the diffusivities $\lambda_{\perp}$ and $\lambda_{\parallel}$ can change independently as well. Increased perpendicular diffusivity ($\lambda_{\perp}$) has been associated with demyelination without increased parallel diffusivity ($\lambda_{\parallel}$) (Song et al, 2002). On the other hand, Beaulieu (2002) argues that the cell membranes and not the myelination play the primary role in restricted perpendicular water perfusion. Wheeler-Kingshott and Cercignani (2014), however, advice against labelling any changes in parallel and perpendicular diffusivities as exact measures for axial degeneration or myelin/membrane damages. Nevertheless, even though we cannot use the eigenvalues as equivalents of either axonal or myelin damage, they can be used as a comparison for overall microstructural WM changes between groups.

Our findings of WM changes in the genu of the CC are consistent with previous studies in MA dependence. Kim et al. (2009) showed higher second and third eigenvalues in the genu of the CC in MA dependence compared to controls. This is in line with our finding of increased $\lambda_{\perp}$ as the mean of the second and third eigenvalue and increased MD. Contrary to other studies (Kim et al., 2009; Salo et al., 2009; Tobias et al., 2010), decreased levels of FA were not found in the genu of the CC (see possible explanation above). Similar results of altered WM integrity in the genu of the CC is also shown in other substance dependences like cocaine (Bell et al., 2011; Lane et al., 2010; Moeller et al., 2005).

To my best knowledge, this study is the first to show WM changes in the right hippocampal region of the cingulum in MA dependence. However, it is difficult to compare our findings of altered WM integrity in the CgH to other studies because of different segmentation procedures. As described above, the JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) divides the cingulum into a part adjacent to the CC (CgC) and a part from the splenium of the CC inferior reaching into the hippocampal area of the temporal lobe (CgH).

The right CgH has been linked to substance related problems in maltreated children in a study by Huang et al. (2009). In their longitudinal study, they showed that adolescents who developed substance dependence had lower FA in the right CgH compared to healthy control subjects.

Previous studies showed impaired WM in the anterior cingulum, which we labelled CgC, throughout diverse substance dependences (Bell et al., 2011; Harris et al., 2014; Lebel et al.,

2013; Moreno-López et al., 2012; Pfefferbaum et al., 2009; Sekine et al., 2006). This is not surprising given its role in the reward system in the brain. I also found a significant decrease of FA in the left CgC in the MA group compared to controls but the results did not survive correction for multiple comparison.

In this study, I did not find WM differences in the uncinate fasciculus between the two groups. This connection between the PFC and the amygdala has not been linked to WM damages in MA dependence before, but impaired WM integrity has been noted in several psychiatric disorders with increased levels of aggressive behaviour (Craig et al., 2009; Passamonti et al., 2012; Sundram et al., 2012). On the other hand, Beyer et al. (2014) could also not show a significant correlation between WM changes in the uncinate fasciculus and aggression in healthy participants.

Behavioural measures

In line with other studies (Cartier, Farabee and Prendergast , 2005; Lapworth et al., 2009; Payer et al., 2011; Plüddemann et al., 2010; Sommers & Baskin, 2006; Zweben et al., 2004), I found higher aggression levels in individuals with MA dependence compared to controls. Especially on the Anger and Physical Aggression subscales, individuals with MA dependence showed higher scores than healthy controls. Physical Aggression and Anger in particular, have frequently been linked to substance abuse in previous studies (Chermack et al., 2001; Fals-Steward et al., 2002; Murray et al., 2008).

Nevertheless, no conclusive statements regarding causality can be made regarding these findings. Aggressive behaviour, especially Physical Aggression and Anger, are multifactorial phenomena. The social and environmental context, childhood and family history of violence and abuse, and the direct effects of MA have to be taken into consideration. Higher levels of anger may be a reason to take MA rather than a result of the drug use. Thus, studies of childhood maltreatment revealed higher levels of Anger and Physical Aggression in these adolescents and as a consequence of that, drug use (Haight et al., 2010).

MA dependence and aggressive behaviour are without a doubt interdependent. An impulsive or more aggressive personality style or an environment, which evokes aggressive behaviour and gives easy access to the drug, are contributing factors for initiating MA use. Especially in poorer communities were crime and violence levels are higher from the start and the illicit

drug market is thriving, individuals with drug abuse are more likely to be drawn into dangerous situations and therefore behave aggressive. Drug-related aggression may further be caused by dealing with gangs independent or related to the dealer, getting money for the drugs by stealing or prostitution, or fighting over the drug itself. A study conducted by Cohen et al. (2003) showed that 80% of women reported violence or abuse from their partners who were using MA. Cohen et al. concluded that interpersonal violence is part of the "lifestyle" of the MA abusing cohort they were studying.

Additionally, the acute psychomotor effects of the drug like sleep deprivation, agitation, paranoia and physical activation may further diminish MA user's ability to make planned and thoughtful decisions and therefor lead to situations where they react impulsive and aggressive.

On the other hand, animal studies have indicated that MA has a direct effect on behaviour. Studies showed increased aggressive behaviour in mice after chronic administration of MA (Crowley et al., 1972; Sokolov, Schindler & Cadet, 2004). Of course, findings in animal studies cannot always be directly extrapolated to humans. However, Murray et al. (2008) found a direct relationship between frequency of drug use and frequency of aggressive behaviour in individuals with substance dependence. In addition, Sommers, Baskin & Baskin-Sommers (2006) found that half of all individuals with MA abuse who showed aggressive behaviour had not committed an aggressive act prior to using MA, supporting the theory that MA directly causes aggression. Ultimately, longitudinal studies are needed to assess fully the causal relationships between substance use and aggressive behaviour.

Relationship between WM alterations and aggression

Although other studies have linked impaired WM integrity in frontal regions to aggressive behaviour (Hoptman et al., 2002; Ruesch et al., 2007; Peper et al., 2014; Saxena et al., 2012), correlational analysis between DTI measures and aggression scores showed no statistical significance in this study.

However, in line with our findings, Tobias et al. (2010) could not find a significant correlation between FA values in the superior corona radiata in MA dependence and hostility. The corona radiata contains, amongst others, reciprocal connections of the cortex and the limbic structures. Inefficient neuronal communication between the in control and inhibition

involved PFC and the reward related limbic structures might play a role in the deficits in response inhibition and impulsive behaviour seen in MA abuse. Jacobus et al. (2013) showed that poorer WM integrity in the superior corona radiata predicted risky behaviour like substance abuse in a longitudinal study with adolescents compared to controls. Furthermore, Zhang et al. (2014) found a relationship between FA in the superior corona radiata and higher impulsivity levels in adolescents with conduct disorder using DTI.

Diverse findings exist for the genu of the CC and its relationship with aggression. Previous studies found an association between altered CC structure and aggressive or violent behaviour (Hoffman & Schutter, 2009; Raine et al., 1997; Zhang et al., 2014). Nevertheless, a DTI study by Saxena at al. (2012) only found trend significance in the correlation between aggression and FA in the genu of the CC in a study group of adolescents with bipolar disorder. Raine et al. (1997) argues that impaired CC function might not be the main structure underpinning aggressive behaviour but may contribute to limbic and cortical dysfunctions.

The CgH, which showed WM abnormalities in the MA group, plays a well-documented role in emotion regulation. Kim et al. (2011) showed in an fMRI study hyperactivation of the posterior cingulum and parahippocampal gyrus in an emotion-matching task in a group of individuals with MA abuse compared to controls. They outline the association of these regions with episodic memory. Since MA abuse is associated with more interpersonal violence, fearful faces may trigger emotional memories in MA users. Kim et al. argued that altered interpersonal communication due to misinterpreted facial expression as social clues, could lead to aggressive or hostile behaviour in MA abuse. In this regard, Payer et al. (2011) similarly showed that individuals with MA dependence demonstrate impaired interpretation of social clues in another facial affect matching task in an fMRI study. Although they showed hyperactivity in the anterior cingulum and not in the posterior, it is interesting to note that these changes were accompanied by high self-ratings of hostility.

This study showed several impaired WM structures in individuals with MA dependence. Aggressive behaviour is a complex phenomenon and is likely to be regulated by a network of underlying brain centres. Therefore, aggression likely cannot be reduced to processes occurring in one single brain area. More likely, altered functional connectivity of emotion regulating centres may play a role in the reduced inhibitory control, impulsivity, and aggressive behaviour seen in MA dependence (Davidson, Putnam & Larson, 2000; Geen,

2001; Grafman et al., 1996). Our findings include WM alterations in connections of the PFC and limbic regions. The PFC executes complex cognitive control, which implicates control over behaviour and decision-making (Coutlee & Huettel, 2012; Heatherton & Wagner, 2011; Ridderinkhof et al., 2004). In their review of PFC control and function, Coutlee and Huettel (2012), emphasize the importance of the PFC for "self-control", more specifically in "response inhibition, delay of gratification, and thought suppression", important factors in aggressive behaviour as well as in drug abuse. In contrast, the subcortical limbic structures are involved in impulsive, affective and reward orientated behaviour (Morgane, Galler & Mokler, 2005). Thus, loss of regulatory control of the PFC over limbic structures may be a possible explanation for the disinhibited behaviour reported in MA dependence.

The general aggression model has two presumptions. An individual needs emotional insight and cognitive control to react towards its environment in a thoughtful manner (Anderson & Bushman, 2002). As shown in previous studies, executive function in individuals with MA dependence can be impaired (Chung et al., 2007; Kim et al., 2009; Salo et al., 2009). In addition, Payer et al. (2011) showed that individuals with MA dependence have poorer emotional insight than controls correlating with higher aggression scores. MA users tend to have diminished emotional insight as well as reduced cognitive capacity, which makes it difficult for them to respond appropriate in situations, which might be dangerous and might provoke aggressive behaviour.

Lastly, since we did not find a significant correlation between WM differences and aggression, this study cannot support any evidence for hemispheric differences in aggressive behaviour.

Limitations

The present study has a number of limitations. First, the measure for aggression levels used in this study is a self-report questionnaire. Although other studies have shown that the self-report measures in substance dependent participants tend to be valid (Darke, 1998), it is not clear that in our study the questions were answered without bias. This might either be due to participants answering questions as they think it is social desirable (Becker, 2007) or simply that the perception of personal behaviour might differ from the actual one.

The second limitation is the different times of MA abstinence, duration of MA use, quantity of MA use and age of substance abuse onset in our study cohort. These differences have been shown to influence WM integrity and therefore DTI measures. Quantity of MA use in particular is difficult to assess because the participants themselves often do not know the exact amounts of MA taken over time. Additionally, MA, which is bought on the street from different dealers, often is diluted with other substances. Different times of drug abstinence have a large influence on WM integrity as shown by Bell et al. (2011). The authors found that with prolonged abstinence from cocaine WM integrity in some brain regions improved.

The third limitation lies within the DTI analysis itself. In case of very small WM pathways, meaning when a fibre is smaller than a voxel itself, it is difficult to determine whether a change in FA is due to WM integrity loss or if the voxel contains other brain tissue, which would alter the results (Smith et al., 2006). However, our ROI results in the CC and cingulum are likely due to an existent reduction in WM integrity because they are major WM tracts. Additionally, the TBSS results in the right superior corona radiata showed a relatively big cluster, so that mixed tissue effects would be unlikely. Furthermore, we used thresholding at 0.2 to avoid exactly this effect. Another limitation of DTI is areas of crossing fibres. As discussed above, in these areas measures like FA have to be interpreted carefully. Increase or decrease of FA can be due to an altered fibre orientation but does not have to include fibre damage.

The fourth limitation is the cross sectional design of our study. Changes in WM integrity could already be pre-existing and not a result of the MA use. Ersche et al. (2013) found brain changes in healthy individuals, which they shared with their cocaine dependent siblings. They found increased impulsivity and compulsivity in both groups and increased volume in striatal-limbic structures.

Fifth, we found significant differences in levels of education, methaqualone and tobacco use in our two groups. These are confounding factors, which all seem to have an influence on brain structure and function. Acute and chronic tobacco use has been shown to influence WM integrity (Kochunun et al., 2013; Savjani et al., 2014). Additionally, Dunst et al. (2014) showed that levels of the Intelligence Quotient (IQ) correlate positively with WM integrity in men but not in women. To my best knowledge, there are no DTI studies in methaqualone use so far but there might be a possible impact of methaqualone on WM integrity. MA and

methaqualone are commonly used together - MA in the mornings and methaqualone in the evening to induce sleep. Therefore, recruitment of individuals with MA dependence without use of methaqualone proved to be almost impossible. We tried to limit the confounding factor by excluding methaqualone dependence.

Sixth, the sample size in this study is rather small. This might have the effect that lack of findings might be a false negative result. Power calculation was done beforehand but estimations for effect size were higher than the results show. Therefore, more participants should have been included.

Finally, we used very stringent inclusion and exclusion criteria; therefore, our cohort might not represent the majority of individuals with MA dependence. We excluded for example any history or current depressive episodes which occur frequently especially in recently abstinent MA users.

Relevance

This study is relevant for the individual MA user, the communities, which struggle with violence and the illicit drug markets, and the state that is paying for law enforcement and other consequences of illegal drug use.

Aggressive individuals with substance dependence are more likely to have more severe dependence symptoms then there non-aggressive counter parts (Bye, 2007; Chermack, Fuller & Blow, 2000).They also seem to have more comorbidities due to drug use and more injuries (Macdonald et al., 2003; Murray et al., 2008). Moreover, aggression levels seem to influence treatment outcome of individuals with drug abuse considerable (Larimer, Palmer & Marlatt, 1999; Schneider & Timko, 2009; Walton, Chermack & Blow, 2002). Anger in particular is linked to high rates of relapse rates, as drug abuse can be a coping strategy for emotional conflicts (Klee & Reid, 1998). Therefore, individuals with substance abuse who also show elevated aggression levels should be referred for intensified treatment concentrating on behavioural coping strategies.

Restoring WM integrity could be a target in substance dependence treatment. It is found that that treatment outcome is associated with WM integrity in cocaine dependence and psychosis (Marques et al., 2014; Xu et al., 2010). Previous studies in animals and humans

have suggested that WM integrity could be partly restored by targeted treatment (Franco et al., 2008; Harsan et al., 2008; Schlaug, Martina & Norton, 2010). A possible mechanism to restore WM integrity could be achieved through cognitive remediation.

The so-called cognitive enhancement or remediation is a process of repeated stimulation of targeted cognitive functions to improve cognitive performances (Robertson & Murre, 1999). This can be achieved by computer-based programs, pharmacological, synchronised movements, physical therapy - or any form of repetitive exercise depending on the specific pathway to be strengthened. Positive results of computer-based cognitive rehabilitation were shown in other psychiatric disorders like schizophrenia or depression (Elgamal et al., 2007; Penadés et al., 2013). Furthermore, Penadés et al. (2013) showed increased WM integrity in schizophrenic patients who underwent cognitive training correlating with cognitive improvement compared to healthy controls.

As discussed above MA dependence can lead to cognitive impairments, which can complicate treatment. Patients in therapy need their cognitive ability and flexibility to process and adapt newly learned behavioural and psychological strategies. Therefore, computer-based rehabilitation programs which concentrate on improving cognitive impairments seen in MA dependence like attentional set-shifting, perseveration, action inhibition, impulsivity and decision making could help patients in treatment (Vocci, 2008).

Strengthening WM pathways between the PFC and subcortical limbic structures might help gaining self-control over impulsive and immediate reward orientated behaviour and thus result in better treatment outcome.

Future research

Resulting from the limitations of this study, future research should concentrate on standardizing drug measurements. A possibility would be splitting the group into subgroups of different age started/ duration/ quantity of drug use/ abstinence times and then correlating the findings. A costly alternative would be doing hair sample analysis to verify drug use statements.

Investigating the different effects of MA on gender would be interesting since previous research found a protective effect of oestrogen on neural cells in animal studies (Culmsee et al., 1999; Dluzen, 2000). Furthermore, oestrogen was found to protect female mice against the neurotoxic effects of MA (Dluzen & McDermott, 2002; Liu & Dluzen, 2006; Myers, Anderson & Dluzen, 2003). Additionally, a study by Peper et al. (2014) found associations

between increased testosterone levels in adolescents and decreased WM integrity in the fronto-temporal-subcortical network. This shows that sex steroids might influence WM integrity and vulnerability in gender.

In addition to using the Buss & Perry Questionnaire, future researchers should try to implement supplementary measurements of aggressive behaviour. These could be for example: conducting interviews with parents, partners or friends and neuropsychological testing. These reports could furthermore help with identifying a cause-effect relationship – stating if the participant showed aggressive behaviour even before the drug use or if the behaviour changed.

For acquiring cause-effect answers though, a longitudinal study would be essential. This could determine if WM changes result from MA use or if WM impairment could also lead to addiction, as well as for the answer if aggression is a cause or effect of drug abuse.

5. Conclusion

This study provides evidence of WM differences between abstinent individuals with MA dependence and healthy controls. Moreover, higher aggression levels in the MA group were found. However, there was no significant association between WM changes and aggressive behaviour scores, perhaps reflecting a number of limitations in this study. This may also indicate that the neurobiology of aggression is not simply correlated with WM damage but is more complex. The non-significant correlation could suggest that additional factors other than MA, like genetic or socioeconomic circumstances, influence their relationship.

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Appendix

Buss & Perry Questionnaire

Instructions: Using the 5 point scale shown below, indicate how uncharacteristic or characteristic each of the following statements is in describing you. To place your rating for each question, circle the number that best describes how you feel.

1 = extremely **un**characteristic of me
2 = somewhat **un**characteristic of me
3 = neither uncharacteristic nor characteristic of me
4 = somewhat characteristic of me
5 = extremely characteristic of me

	Extremely uncharacteristic	Somewhat uncharacteristic	Neither nor	Somewhat characteristic	Extremely characteristic
1. Some of my friends think I am a hothead.	**1**	**2**	**3**	**4**	**5**
2. If I have to resort to violence to protect my rights, I will.	**1**	**2**	**3**	**4**	**5**
3. When people are especially nice to me, I wonder what they want.	**1**	**2**	**3**	**4**	**5**
4. I tell my friends openly when I disagree with them.	**1**	**2**	**3**	**4**	**5**
5. I have become so mad that I have broken things.	**1**	**2**	**3**	**4**	**5**
6. I can't help getting into arguments when people disagree with me.	**1**	**2**	**3**	**4**	**5**
7. I wonder why sometimes I feel so bitter about things.	**1**	**2**	**3**	**4**	**5**
8. Once in a while, I can't control the urge to strike another person.	**1**	**2**	**3**	**4**	**5**
9. I am an even-tempered person.	**1**	**2**	**3**	**4**	**5**
10. I am suspicious of overly friendly strangers.	**1**	**2**	**3**	**4**	**5**
11. I have threatened people I know.	**1**	**2**	**3**	**4**	**5**
12. I flare up quickly but get over it quickly.	**1**	**2**	**3**	**4**	**5**
13. Given enough provocation, I may hit another person.	**1**	**2**	**3**	**4**	**5**
14. When people annoy me, I may tell them what I think of them.	**1**	**2**	**3**	**4**	**5**

	Extremely uncharacteristic	Somewhat uncharacteristic	Neither nor	Somewhat characteristic	Extremely characteristic
15. I am sometimes eaten up with jealousy.	**1**	**2**	**3**	**4**	**5**
16. I can think of no good reason for ever hitting a person.	**1**	**2**	**3**	**4**	**5**
17. At times I feel I have gotten a raw deal out of life.	**1**	**2**	**3**	**4**	**5**
18. I have trouble controlling my temper.	**1**	**2**	**3**	**4**	**5**
19. When frustrated, I let my irritation show.	**1**	**2**	**3**	**4**	**5**
20. I sometimes feel that people are laughing at me behind my back.	**1**	**2**	**3**	**4**	**5**
21. I often find myself disagreeing with people.	**1**	**2**	**3**	**4**	**5**
22. If somebody hits me, I hit back.	**1**	**2**	**3**	**4**	**5**
23. I sometimes feel like a powder keg ready to explode.	**1**	**2**	**3**	**4**	**5**
24. Other people always seem to get the breaks.	**1**	**2**	**3**	**4**	**5**
25. There are people who pushed me so far that we came to blows.	**1**	**2**	**3**	**4**	**5**
26. I know that “friends” talk about me behind my back.	**1**	**2**	**3**	**4**	**5**
27. My friends say that I’m somewhat argumentative.	**1**	**2**	**3**	**4**	**5**
28. Sometimes I fly off the handle for no good reason.	**1**	**2**	**3**	**4**	**5**
29. I get into fights a little more than the average person.	**1**	**2**	**3**	**4**	**5**

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

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

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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 tasks 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 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 any thing 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

1. 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

2. 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

3. 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

4. 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