Neural correlates of deficits in affect regulation in methamphetamine dependence with and without a history of psychosis

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Abstract

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Methamphetamine dependence has been associated with neurological damage resulting in potentially long-lasting changes in cognitive-affective processes, a range of behavioral problems and psychiatric disorders, including psychosis. Poor emotional control and maladaptive social behaviors have been linked to abnormalities in brain function and structure. However, the links between alterations in neurocircuitries, affect dysregulation, and psychotic symptoms in methamphetamine dependence are yet to be fully elucidated.

This project aimed to delineate emotion regulation capabilities as well as brain structure and function in methamphetamine-dependent individuals, patients with a history of methamphetamine-associated psychosis, and healthy adults. The four cross-sectional studies presented here investigated socio-emotional behaviour using self-report questionnaires and social cognition tasks; and assessed neural activation during incidental emotion regulation, measured in an affect labelling task as part of functional magnetic resonance imaging. Additionally, structural magnetic resonance imaging and diffusion tensor imaging were employed to determine grey matter and white matter structural abnormalities, respectively, and to correlate findings with the presence/absence of affect dysregulation and psychotic symptoms.

Both methamphetamine-dependent groups showed deficits in emotion regulation abilities, as evidenced by increased levels of aggression, impulsivity, and emotion reactivity. Further, social cognition capacities, including recognising emotions and inferring mental states of others, were diminished in both groups, with greater functional decrements in patients with methamphetamine-associated psychosis. These patients further demonstrated grey matter loss in frontotemporal brain regions and hippocampi, as well as globally reduced white matter integrity, compared to

methamphetamine-dependent individuals; and structural deficits in prefrontal and temporal brain regions were associated with impaired affect regulation. Frontolimbic hypoactivation during emotion perception further suggests a role of diminished emotional salience attribution in the pathogenesis of methamphetamine-associated psychosis. Whereas methamphetamine-dependent individuals displayed prefrontal hyperactivation during affect labelling, potentially reflecting a compensatory activation to sufficiently regulate affect, or suggesting a cognitive bias towards the negative facial emotions.

Longitudinal data and prospective research designs are needed to address the issue of causality as well as the issue of changes in brain structure and function over time as addiction and related psychopathology progress. Therapies targeting socio-emotional perception and affect regulation skills ultimately may help improve social functioning and mitigate relapse rates.

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Chapter 1

Introduction to the study

1.1. Study rationale

Methamphetamine (MA) abuse has been a serious problem in South Africa, in particular the Western Cape, for many years now and is cause for concern for a number of reasons. MA is a highly addictive synthetic psychostimulant and local studies have reported a huge increase in the number of MA-related admissions to drug treatment facilities over the last few years (Plüddemann et al., 2008; 2013). The latest reports from the Medical Research Council's South African Community Epidemiology Network on Drug Use (SACENDU) indicated that 33% of patients seeking treatment used MA as their primary drug of choice (Johnson et al., 2014). The detrimental effects, both medical and psychiatric, of MA are extensive, and given the poor treatment engagement and high relapse rates in MA addiction, more information is needed for the development of viable treatments (Rawson et al., 2002).

Numerous preclinical and clinical studies have demonstrated that MA exposure results in extensive neural damage, especially in the dopamine neurocircuitry (Barr et al., 2006; Krasnova & Cadet, 2009). This neural damage may, in turn, underlie an increased risk of mental health problems, including depression, anxiety and psychotic symptoms, which commonly manifest in paranoia, persecutory delusions and hallucinations (Grant et al., 2012; McKetin et al., 2006; Zweben et al., 2004). It has been shown that the prevalence of psychosis among MA abusers was up to eleven times higher (13 % versus 1.2 %) than that seen among the general population (Akindipe et al., 2014; McKetin et al., 2006). Moreover, MA dependence is characterised by cognitive-affective impairment (Kim et al., 2011a), reduced inhibition and consequently, unstable interpersonal relations (Homer et al., 2008;

Lapworth et al., 2009), severely affecting the individual and their social environment. Studies have repeatedly reported a constellation of behavioural problems in MA-dependent individuals, including high rates of impulsivity and aggression (Dawe et al., 2009; Payer et al., 2011; Plüddemann et al., 2010). Such behavioural and affective changes have been shown to impact on entire communities by leading to negative social outcomes like social withdrawal/rejection or increased rates of crime, including physical and sexual violence (Sommers and Baskin, 2006; Watt et al., 2014). Furthermore, it is notable that emotional and cognitive impairments as well as psychotic symptomatology have been identified as contributing factors to high relapse rates in MA addiction (Rawson et al., 2002). The assessment of underlying neural substrates of the described behavioural-affective impairment in MA-dependent individuals with and without a history of psychosis forms the focus of this thesis.

Individuals who abuse MA can suffer long-lasting brain injury (Marshall & O'Dell, 2012), and grey and white matter brain abnormalities have consistently been reported in MA-dependent individuals (Berman et al., 2008; Chang et al., 2007). Yet, the findings are divergent and inconsistent, and comparatively little data exists for individuals who have developed psychotic symptoms as a result of MA dependence. Only two studies have assessed grey matter structures in patients with MA-associated psychosis (MAP) and reported volume reductions in the amygdala and hippocampus (Aoki et al., 2011) as well as in perisylvian structures and frontopolar cortices (Orikabe et al., 2013) relative to healthy controls. One molecular imaging study identified poor neural integrity in frontal brain areas in both individuals with MA dependence and MAP. Structural brain changes in the former group generally comprised decreased grey matter volumes and impaired white matter integrity in frontotemporal brain areas, in addition to larger grey matter volumes of striatal structures (Berman et al., 2008; Chang et al., 2007). Many of these MA-associated brain structure deficits, particularly in the frontal lobe, have previously been associated with impairment in cognitive control (London et al., 2014). But very little research has been done on the neural substrates of affect regulation in these cohorts, despite the fact that several of the identified brain regions affected by MA abuse, including the anterior cingulate cortex, prefrontal cortex, superior temporal gyrus, insula and amygdala (Berman et al., 2008; London et al., 2014) have also been shown to be major role players in emotion processing and regulation (Davidson et al., 2000; Kohn et al., 2014; Phillips et al., 2003a).

Thus, it is not clear what causes some individuals to present with particular behavioural and psychiatric problems described in MA dependence, nor are the links between neurocircuitry alterations, emotional dysregulation, and psychotic symptoms fully understood. Impaired ability to regulate emotional responses has previously been linked to drug addiction and aggressive behaviour (Bradley et al., 2011), and one can argue that the social problems observed in MA-dependent individuals may arise from impaired emotion regulation. Furthermore, emotion dysregulation and psychiatric symptoms may have an adverse effect on treatment outcomes. However, there is a paucity of research delineating the extent and functional consequences of MA-related deficits in emotion regulation in relation to underlying neural substrates. Particularly little research has been conducted in MAP to date and the current research project attempts to address this shortcoming.

1.2. Study objectives

The present neuroimaging project aims to a) investigate affect regulation and social cognition and their relationship in MA dependence and MAP, b) examine changes in brain structure and function resulting from MA dependence in these populations, c) assess the extent to which the observed brain deficits are associated with affect regulation abilities, and d) determine the degree to which the observed structural and functional changes differentially underpin psychotic symptoms. To achieve these aims, I compare the performance of adult MA-dependent individuals with and without a history of psychosis with neurologically healthy participants on structural and functional neuroimaging protocols as well as on behavioural tests and questionnaires.

The study employs multiple types of neuroimaging applications, including diffusion tensor imaging (DTI) to assess white matter integrity, structural magnetic resonance imaging (MRI) to evaluate structural grey matter impairment, and functional magnetic resonance imaging (fMRI) to investigate neural substrate dysfunction in the corticolimbic circuit during an incidental emotion regulation task. It further assesses behavioural and interpersonal deficits in MA-dependent individuals, including aggression, impulsivity, social cognition, and self-report difficulties in emotion regulation. Exploring possible associations between brain alterations, psychotic symptoms, and affect dysregulation can not only provide opportunities for a better understanding of the underlying mechanisms of the affective and psychiatric pathology in MA-dependent individuals, but also provide therapeutic targets.

1.3. Study details

The study was approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (HREC/REF: 692/2013 linked to umbrella study HREC/REF: 340/2009) and complied with ethical guidelines established by the Declaration of Helsinki (World Medication Association, 2013). After a detailed description of the study, all participants gave written informed consent (form attached in appendix). It was explained that participation was entirely voluntary and consent could be withdrawn at any time during participation. All information was kept confidential, and study documentation used codes instead of names for further processing. On completion of the study, participants were compensated with food vouchers for a local supermarket.

Sixty-four participants were enrolled in this research project, completing the different sections of neuroimaging and behavioural testing (with some exceptions as indicated in the respective studies). One additional participant had to be excluded from the project, as a neurological abnormality was detected. Further, a recent research study in the Department of Psychiatry indicated that a sample size of 20 is not sufficient to detect group differences in white matter integrity with the chosen scan parameters. Therefore, while data analyses for study 1, 2 and 4 were underway, additional DTI data were collected, resulting in an overall sample of 109 participants in study 3.

Throughout this thesis, participants in the two MA-dependent study groups are termed individuals with MA dependence and patients with MAP; however, it is important to note that both groups included short- to medium-term abstinent former users and some active users as well. Specific details on this variable are given in each study of this thesis.

South Africa is a nation of diversity with people coming from various ethnic backgrounds; this also applies to the research participants of this project, indicating ethnic origins as African, Indian and mixed ancestry. As this project does not aim to study potential ethnical influences on MA-related brain changes and affect dysregulation, no specific details on ethnicity of the research participants are given in the respective chapters. However, participants in each group are matched as closely as possible in terms of ethnicity to account for the potential confounding effects.

1.4. Dissertation layout

This thesis includes four independent chapters, describing the experimental research, together with a comprehensive literature review, discussion and conclusion. The chapters concerning the different studies have been prepared as manuscripts for submission to scientific journals for publication after submission of this thesis. One manuscript, chapter four, has already been submitted to an international journal and is currently under review. None of this work has been published elsewhere before. Due to this layout, it is inevitable that some repetition of information on background, methodology, and study limitations occurs in the separate chapters. However, I will try to minimise this as far as possible.

In the following chapter, an overview of relevant literature and background information on MA addiction is provided. First, the neurotoxic effects of MA on the central nervous system are highlighted. While it is important to discuss molecular and cellular bases of MA-induced neuropathologies, providing extensive detail is beyond the scope of this thesis and the reader is referred to the several excellent reviews cited in the chapter. This is followed by addressing how MA abuse is associated with psychotic symptoms and behavioural problems; and a brief overview on research in affect regulation is given. Although various imaging modalities have been applied in MA research, the final part of this chapter reviews the most relevant research findings from MRI, fMRI and DTI studies on MA-related structural and functional changes in the brain. The third chapter describes the investigation of behavioural changes, indicated by self-reported aggression, and social cognition deficits, evidenced by impaired facial emotion recognition and theory of mind skills in MA dependence and MAP; while their potential influence on the social disturbances in MA addiction is discussed. In chapter four, grey matter brain alterations in frontotemporal and subcortical brain regions, assessed with MRI, and their association with self-report deficits in affect regulation are described in MA dependence and MAP. Chapter five describes microstructural white matter changes, investigated with DTI, and how they may be linked to impulsivity in MA dependence and MAP. Chapter six describes an fMRI examination of functional deficits in neural correlates of emotion processing and incidental emotion regulation in MA dependence and MAP. A comprehensive discussion is given in chapter seven that summarises the main findings of the work, highlights limitations and presents conclusions. Attached in the appendix are the questionnaires employed in the different studies as well as the participant informed consent form.

Chapter 2

Literature Review

2.1. Introduction to methamphetamine addiction

Methamphetamine (MA) is a highly addictive psycho-stimulant, known for its euphoriant but potent reinforcing properties (Volkow et al., 2001), with these effects being mediated through activation of the reward- and affect-related areas of the mesolimbic and mesocortical pathways (Goldstein & Volkow, 2002; Völlm et al., 2004). Especially the dopaminergic projections from the ventral tegmental area (VTA) to the ventral striatum (nucleus accumbens, NAc), amygdala and hippocampus play a role in drug-related memories, conditioned responses and drug-seeking behaviour (Koob & Le Moal, 2001). The other pathway, critical in acute reward and the initiation of addiction, comprises projections from the VTA to the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Kalivas & Volkow, 2005). While the NAc is primarily involved in the modulation of motivational salience and expression of reward-motivated behaviours, the OFC and ACC are thought to regulate behavioural response intensity and are activated during intoxication, craving and bingeing (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; Kalivas & Volkow, 2005). The ACC, in particular its ventral part, shares extensive connections with the amygdalae, hypothalamus, the NAc, and insular cortex, and is involved in the emotional aspects of self-regulation (Bush et al., 2000).

When frequent MA consumption occurs, the powerful stimulation of the reward circuit can alter various neurotransmitter systems; and MA’s neurotoxic effects lead to long-term monoamine depletion of the brain together with neuron terminal degeneration (Krasnova & Cadet, 2009). These neuroadaptive functional and structural changes may, in turn, result in abnormalities in reward processing, impaired response inhibition, and drug seeking behaviour (Goldstein & Volkow, 2002; Kalivas & Volkow, 2005; Koob & Le Moal, 2001). These features promote ongoing MA use to compensate for the monoaminergic deficits, evidenced by fatigue and anhedonia; a critical step in the development of addictive processes (Barr et al., 2006; Volkow et al., 2002). Consequently, repeated use of the substance can rapidly escalate, involving the development of tolerance for MA and resulting in binge use and dependence (Goldstein & Volkow, 2002).

The multiple neurobiological impacts of MA dependence on the nervous system and adverse consequences in behaviour and mental health will be discussed in the following sections.

2.2. Neurotoxic effects of methamphetamine

MA falls under the phenylethylamine class of psychostimulants and its high lipid solubility allows for it to rapidly breach the blood-brain barrier (Barr et al., 2006). Its comparatively high half-life of approximately ten hours leads to longer lasting behavioural and psychological effects than those of other stimulants (Barr et al., 2006; Cruickshank & Dyer, 2009). The structural homology between MA and the body's endogenous monoamines allows the drug to enter nerve terminals and substitute for these monoamines (Marshall & O'Dell, 2012). Therefore, the pathophysiology of methamphetamine is based on its impact on multiple neurotransmitter systems, including the dopamine, norepinephrine, glutamate, and serotonin systems (Yamamoto et al., 2010). Consequently, transmitter release through several mechanisms of action contributes to MA's neurotoxicity. MA contributes to the release of monoamines from storage vesicles into the cytoplasm and can cause a reverse transportation of monoamines from the cytoplasm into the synaptic cleft, while concurrently, reuptake mechanisms of monoamines into the cytoplasm and vesicles are inhibited (Krasnova & Cadet, 2009). Acutely, this increase of extracellular neurotransmitter results in the initial euphoric sensation, increased vigilance and hyperactivity. However, repeated use can lead to widespread neuronal damage and a number of adverse physiological and neurological consequences (Marshall & O'Dell, 2012; Yamamoto et al., 2010).

Following the monoamine surplus, a number of events can cause neurotoxicity and consequent brain injuries, but the exact process is not yet known. Several different mechanisms have been identified, including oxidative stress, mitochondrial and endoplasmic reticulum dysfunction, excitatoxicity, hyperthermia, blood-brain barrier dysfunction, and inflammation (Krasnova & Cadet, 2009; Yamamoto et al., 2010). All of these cannot be discussed here, but some insight is provided. One of the main contributing mechanisms seems to be the generation of free radicals, including reactive oxygen species (Davidson et al., 2001). This is caused by either enzymatic breakdown or autoxidation of dopamine, and can eventually overpower the cell's antioxidative systems in place. The resulting oxidative stress may consequently damage cell DNA, protein and lipid components and lead to neuronal apoptosis (Krasnova & Cadet, 2009). Further production of reactive oxygen and nitrogen species can be, among many other mechanisms, the result of MA-induced increases in extracellular glutamate concentrations and subsequent NMDA receptor activation and intracellular calcium influx (Marshall & O'Dell, 2012). Also, some reactive species are generated through microglial activation, another possible mechanism associated with MA-induced neurotoxicity (Yamamoto et al., 2010). Microglia are immune cells within the nervous system and are activated during neurodegenerative processes (Kreutzberg, 1996). Frequent MA use, however, has been shown to overactivate microglia in the striatum, thalamus, midbrain, and orbitofrontal and insular cortices (Sekine et al., 2008), which in turn, leads to the release of inflammatory mediators and can result in neuronal damage through inflammatory processes (Krasnova & Cadet, 2009).

Taken together, long-term MA use acts on many molecular pathways forming the mechanistic substrates of inflammation, while causing reductions in neurotransmitter receptors and transporters, and neuron terminal damage - potentially causing persistent monoaminergic, particularly dopaminergic deficits (Marshall & O'Dell, 2012; Krasnova & Cadet, 2009). Supporting this notion are findings from imaging studies using positron emission tomography (PET), which consistently show decreases in dopamine and serotonin transporter and receptor levels in the striatum, and the orbitofrontal and dorsolateral prefrontal cortex of MA abusers, even long after cessation of drug use (Chang et al., 2007; Sekine et al., 2001, 2003, 2006; Volkow et al., 2001). Further evidence emerges from magnetic resonance spectroscopy (MRS) studies, showing reduced levels of neuronal integrity markers in frontal grey matter and white matter, and the basal ganglia (Ernst et al., 2000; Nordahl et al., 2005; Howells et al., 2014).

In line with the described neurotoxic effects on the nervous system, it is of growing concern that prolonged MA abuse may result in long-term psychiatric problems, comprising depression, irritability, anxiety, and thought disorder, among others (McKetin et al., 2006; Salo et al., 2011; Zweben et al., 2004). While a substantial number of MA abusers develops sub-clinical symptoms such as suspiciousness and paranoia (McKetin et al., 2006), the following section of this review will focus on the individuals who develop MA-associated psychosis (MAP).

2.3. Psychiatric effects of methamphetamine

It has repeatedly been stated that frequent use of MA increases the risk of developing psychosis (McKetin et al., 2010), with positive and negative symptoms similar to those seen in schizophrenia (Grant et al., 2012; McKetin et al., 2006; Srisurapanont et al., 2011). Positive symptoms often manifest as visual and auditory hallucinations, delusions, and incoherent speech, while negative symptoms seen in MA abusers comprise flattened affect, impaired speech, and psychomotor retardation (Chen et al., 2003; Srisurapanont et al., 2003, 2011). Such similarity in symptomatology of the two diseases is thought to be related to comparable neuropathological changes in the mesolimbic dopamine system in patients with MAP and schizophrenia (Grant et al., 2012). Recently, however, it has been proposed that MAP involves a combination of dopaminergic, glutamatergic and GABAergic dysfunction, leading to cortical interneuron damage (Hsieh et al., 2014). Although human research to date is very limited, neuroimaging studies have shown that the clinical severity of MAP symptoms correlates with MA-associated neurotoxic effects in both the striatum and the prefrontal cortex (Sekine et al., 2001, 2003). Frontal cortex damage in patients with MAP has further been indicated by grey matter volume reductions (Aoki et al., 2013) and neuronal integrity deficits (Howells et al., 2014).

Overall, there is a paucity of studies examining the potential underlying mechanisms through which MA precipitates psychotic symptoms, but some risk factors for the development of psychosis associated with MA abuse have been identified. In particular, greater severity and duration of drug use, using at a younger age and/or a family history of psychotic disorders, may put the individual at greater risk (Chen et al., 2003; McKetin et al., 2010). Also genetic variants may constitute important risk factors. One gene that may play a role in MA psychosis is the dopamine receptor D2 (DRD2) gene. Its TaqI A polymorphism both regulates prolongation of psychosis symptoms and leads to brain atrophy in the temporal lobe (Harano et al., 2004), and grey matter volume reductions have previously been reported in the superior temporal gyrus of MAP patients (Aoki et al., 2013). Furthermore, the SNCA or alpha-synuclein gene, primarily concentrated in presynaptic nerve terminals, is implicated in the modulation of dopamine transmission and has been associated with MAP (Bousman et al., 2009). The contribution of genetic factors to the vulnerability to methamphetamine abuse and associated psychiatric symptoms has also been observed in the serotonergic system. It has been suggested that prolonged MA use, combined with a specific polymorphism of the serotonin transporter gene (5-HTTLPR), may lead to reduced serotonin levels and receptor-binding potential in the brain, resulting in the dysfunction of the serotonergic system and contributing to the development of MA psychosis (Ezaki et al., 2008). Other gene associations for MAP include DTNBP1 or dysbindin-1, a gene found primarily in axon bundles in the cerebellum and hippocampus; OPRM1, which is coding for the µ-opioid receptor; and SOD2, encoding mitochondrial proteins concerned with oxidative stress response (Bousman et al., 2009).

Psychotic symptoms associated with intoxication or withdrawal typically last a few hours, whereas MAP symptoms usually exceed those and last about a week (Iwanami et al., 1994), with the large majority resolving within one month. Nevertheless, longer-lasting and recurring psychiatric symptoms are not uncommon in MA-dependent patients; occurring even after long-term abstinence from the drug (Deng et al., 2012; Iwanami et al., 1994; Ujike & Sato, 2004). Threatening situations but also mildly stressful experiences, including psychological and physical stress, have been identified as possible precipitating factors in the spontaneous psychosis recurrence and appear to be associated with noradrenergic hyperactivity and increased dopamine release (Yui et al., 2000). Also, severe insomnia and heavy alcohol consumption may induce a recurrent psychotic state after discontinuation of MA abuse (Ujike & Sato, 2004), indicating a long lasting and MA independent vulnerability. As pointed out earlier, not every individual develops psychosis subsequent to MA abuse. Two studies, from Australia and South Africa, have reported a prevalence of psychosis among MA abusers of 13% (Akindipe et al., 2014; McKetin et al., 2006). An American study, following up on individuals three years after treatment for MA dependence, confirmed that 12.7% met criteria of lifetime psychotic disorder (Glasner-Edwards et al., 2010). These numbers illustrate the challenges MA dependence and MAP pose not only on the health sector, but also on communities. Of particular concern are the heightened levels of hostility, including threatening behaviour, assault and the destruction of property observed in individuals who experience psychotic symptoms (McKetin et al., 2008). However, not only are the psychotic symptoms associated with serious social problems (Chen et al., 2003), MA-dependent individuals often develop sub-clinical symptoms that manifest in adverse behavioural changes and lead to impaired social functioning (Homer et al., 2008). MA-associated behavioural and social deficits will be discussed, with a focus on difficulties in affect regulation, in the following section.

2.4. Behavioural effects of methamphetamine

The neurotoxic effects and resulting brain injury associated with MA dependence has been shown to have a range of detrimental consequences, including behavioural deficits, impairment in cognition and motor skills, and enhanced conditioned avoidance responses. While there is a wealth of human research studies on MA-associated cognitive impairments (relating to decision making, attention, mental flexibility and working memory [Hart et al., 2012; Nordahl et al., 2003; Scott et al., 2007]), there is relatively little data on the effects of MA on affect regulation and related behavioural and social problems. There is substantial evidence that affect dysregulation underlies the vulnerability to, as well as the initiation and maintenance of substance use behaviours; and that poor regulation of affect leads to an altered reactivity to environmental cues and behavioural problems (Bradley et al., 2011; Cheetham et al., 2010). The reduced ability to regulate negative, hostile feelings and behaviours is likely to produce a variety of adverse behavioural and affective changes, such as irritability, emotional reactivity, and aggression in MA-dependent individuals (Homer et al., 2008).

Frequently, a large proportion of MA-dependent individuals reported difficulties in controlling their anger - as expressed in aggressive and violent behaviours - with a correspondingly high occurrence of assault and weapons charges (Cohen et al., 2003; McKetin et al., 2006; Sommers et al., 2006; Zweben et al., 2004). A South African study has also shown recent use of MA to be associated with increased levels of aggression and mental health problems in adolescents (Plüddemann et al., 2010). Additionally, a higher incidence of aggressive behaviours is not only evident in individuals who currently use MA, but also in abstinent former abusers (Sekine et al., 2006). Moreover, this PET study showed that reduced serotonin transporter density in the orbitofrontal, temporal, and anterior cingulate areas is closely associated with higher rates of aggression in MA abusers.

It has also been argued that difficulties with impulse control represent one of the major behavioural elements of affect dysregulation (Gratz & Roemer, 2004). Being closely linked to substance abuse, both as a facilitator and as a consequence, impulsivity refers to a collection of maladaptive behaviours that occur irrespective of the potential consequences (de Wit, 2009; Verdejo-Garcia et al., 2008). There is evidence supporting the idea that neuroadaptive changes in the frontostriatal networks contribute to the impaired inhibitory control seen in drug-dependent individuals (Jentsch & Taylor, 1999, Goldstein & Volkow, 2011). As long-term use of MA has previously been linked to high levels of impulsivity (Semple et al., 2005), it may play a major role in the impaired capacity to control or inhibit aggressive impulses observed in MA-dependent individuals (Dawe et al., 2009). Together, these previous research findings suggest a close link between affect dysregulation and impulsivity in MA dependent individuals.

In addition to impulsivity, psychotic symptoms have been identified as mediators between MA dependence and hostility (Lapworth et al., 2009). It has been argued that this is based on the tendency to misinterpret social situations and mistakenly attribute hostile intentions to others (Sommers et al., 2006); consequently perceiving the environment as hostile (Lapworth et al., 2009). Findings of deficits in social cognition skills, evidenced by impairments in emotion recognition, identifying people's mental state, and empathy, provide further support for this notion (Henry et al., 2009; Kim et al., 2010, 2011a). Taken together, emotion dysregulation, paranoid attributions, diminished social competencies, and consequent incapacity to control anger and aggression may therefore underlie the high rates of MA-related antisocial and violent behaviours, and the adverse impact on social support and social networks

(Baicy & London, 2007; Cretzmeyer et al., 2003). Consequently, these findings indicate that efficient emotion regulation is a fundamental prerequisite for healthy social functioning and that MA-related deficiencies impact on general, mental and social wellbeing.

2.5. Affect regulation research

Affect regulation refers to “the process by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions” (Gross, 1998). To consciously increase or decrease emotional response tendencies different strategies can be applied, including positive reappraisal, self-blame, catastrophizing, and suppression. However, emotion regulation may also happen unintentionally, without conscious awareness (Gross, 2002; Hariri et al., 2000), and when successful, it allows the individual to cope with negative situations or maximise positive aspects of experiences (Gross, 1998). Importantly, this conceptualisation emphasises the importance of managing emotions to facilitate adaptive behaviour, motivation, and cognition, rather than controlling the emotion itself (Tamir, 2011). The inability to regulate emotional responses has been associated not only with drug addiction (Cheetham et al., 2010), but also various psychiatric disorders, including depression and schizophrenia (Johnstone et al., 2007; Stegmayer et al., 2014; Taylor & Liberzon, 2007), impulsive aggression (Davidson et al., 2000) and impaired social function (Phillips et al., 2003a). Especially the two latter observations are consistent with the assumption that emotion regulation does not only reside within the individual, but is also a socially constructed process that can shape the social environment (Gross, 2002; Tamir, 2011).

In research studies investigating emotion regulation, participants are typically asked to view either emotionally evocative scenes or facial stimuli, followed by the effort to reframe the emotional content and regulate their responses by deploying specific volitional cognitive strategies, such as reappraisal or suppression. Research employing functional magnetic resonance imaging (fMRI) has demonstrated that task performance produces significant effects on neural systems relevant to both emotion activation and emotion regulation (Kohn et al., 2014; Ochsner & Gross, 2008). Within the former system, the amygdala and insula are crucial for the detection of affective stimuli and the generation and expression of behavioural responses (Adolphs, 2002; Anderson & Phelps, 2002; Phillips et al., 2003a). For example, when participants are instructed to increase their negative emotional responses, an increase in amygdala activity can be detected (Urry et al., 2006). During affect regulation, independent of the study paradigm used, these fMRI studies consistently described increased activity in frontal brain areas and reduced activity in the amygdala and other limbic regions, in addition to changes in self-reported emotions (Kohn et al., 2014; Ochsner & Gross, 2008). In particular, activated frontal areas comprised the anterior and middle cingulate cortex, the lateral and medial prefrontal cortex (PFC), and the OFC (Kohn et al., 2014; Ochsner et al., 2002, 2004; Wager et al., 2008). Interestingly, the dorsolateral PFC has been implicated in regulating cognitive processes, like attention (Kohn et al., 2014); while the ventrolateral and ventromedial PFC is more involved in the regulation of affect (Diekhoff et al., 2011; Hariri et al., 2003; Lieberman et al., 2007). Additionally, the superior and middle temporal gyrus, angular gyrus and supplementary motor area have been associated with a successful regulation of emotions (Kohn et al., 2004; Wager et al., 2008).

In keeping with the findings from studies on conscious emotion regulation, there is emerging evidence that the same neural activation pattern of prefrontal cortical areas inhibiting limbic responses underlies the linguistic processing of emotions (Burklund et al., 2014; Lieberman et al., 2007; Hariri et al., 2000; 2003; Payer et al., 2012). These studies have asked their participants to verbally encode emotional stimuli, referred to as affect labelling, which represents an unintentional form of emotion regulation. Evidence suggesting that the medial PFC mediates the lateral prefrontal-emotional response relationship in both reappraisal and affect labelling (Lieberman et al., 2007; Urry et al., 2006; Wager et al., 2008) lends further support for the notion of shared underlying neural substrates in intentional and incidental emotion regulation. The medial PFC has also been associated with self-referential processing and shown greater activity during the upregulation of negative emotions (Ochsner et al., 2004). In sum, such findings substantiate a top-down circuit of emotion regulation in which several prefrontal regions exert regulatory control over subcortical amygdala pathways (Johnstone et al., 2007; Urry et al., 2006; Wager et al., 2008). In MA dependence, a corticolimbic dysregulation featuring deficits in the top-down control of emotional impulses is thought to manifest due to various functional, structural, and metabolic brain abnormalities (Baicy & London, 2007; Berman et al., 2008). The last section of this chapter will, therefore, review MA-related deficits in grey matter and white matter reported in human research.

2.6. Methamphetamine-related brain alterations

As previously pointed out, a growing body of literature suggests that MA-related abnormalities in the structural and functional integrity of the brain are associated with cognitive deficits (Berman et al., 2008; Scott et al., 2007), but it is less clear how these abnormalities cohere with aberrant affect regulation and socio-emotional processing in MA-dependent individuals.

Regional morphological grey matter changes in MA abuse have been examined in a series of neuroimaging studies with divergent findings of cortical and subcortical volume increases and decreases. However, due to the fact that the drug largely influences dopaminergic neurotransmission, many studies have demonstrated structural changes in brain areas with strong dopaminergic innervations. Specifically, volume reductions in frontal cortical areas and increases in striatal grey matter volumes have been most consistently reported (Berman et al, 2008). One MRI study assessed grey matter structure in the pars orbitalis of the inferior frontal gyrus and affect regulation, using a reappraisal task in MA-dependent individuals, and found both diminished grey matter integrity and task performance relative to healthy controls (Tabibnia et al., 2011). Although neural activation in the pars orbitalis (belonging to the ventrolateral PFC) has previously been shown to correlate with successful emotion regulation (Ochsner et al., 2004; Wager et al., 2008), grey matter deficits did not significantly correlate with reappraisal performance in the MA-dependent individuals. This finding was attributed to a potential disassociation of structural changes in a brain region and its functional activation.

One of the early MRI studies in MA dependence noted broad grey matter deficits in the cingulate, limbic, and paralimbic cortices - regions that have been implicated in emotion regulation (Thompson et al., 2004). In addition, MA abusers, relative to healthy controls, showed bilateral hippocampus volume reductions, which was related to worse memory performance. It has further been shown that MA-related structural grey matter deficits in the right middle frontal cortex (part of the dorsolateral PFC) related to impaired executive functioning (Kim et al., 2006). Interestingly, in participants with long-term abstinence (six months or longer) these effects seemed to abate, suggesting some recovery in grey matter density when abstaining from MA. Further evidence for this notion is given by a study that scanned participants twice, about one month apart, and showed that grey matter volumes in the inferior frontal, angular, and superior temporal gyri, insula, precuneus and occipital pole increased during this period of abstinence (Morales et al., 2012). A similar positive relationship with abstinence was shown for grey matter density in the amygdala, putamen, and left fusiform gyrus (Schwartz et al., 2010). On the other hand, reported reduced grey matter density in the right middle frontal gyrus showed a negative correlation, while bilateral insula volume reductions showed no correlation with abstinence from MA, suggesting that different brain regions may recover at different rates (Schwartz et al., 2010).

Another study which assessed MA-related grey matter deficits was that of Nakama et al. (2011) which found smaller grey matter volumes in the dorsolateral prefrontal, orbitofrontal, prefrontal, and superior temporal cortex in MA-dependent individuals. While aging is generally associated with cortical volume loss this study detected a pattern of greater age-related grey matter loss in MA-dependent individuals compared to healthy controls. This effect was apparent in the frontal, temporal, occipital and insular lobes, suggesting an accelerated in mental functioning. It was proposed that, in particular the volume losses in occipital and temporal cortices are potentially related to co-morbid psychotic features in the MA-dependent group, but the study did not provide relevant data to confirm this notion.

Only two studies to date have assessed grey matter volumes in MA-associated psychosis (MAP) and reported volume reductions in the left posterior inferior frontal and anterior superior temporal gyrus, and bilateral frontopolar cortices (Aoki et al., 2013) in addition to reductions in the bilateral amygdala and hippocampus (Orikabe et al., 2011). While some results were consistent with findings from research in schizophrenia, volume reductions in amygdala and frontopolar cortices were argued to be pathophysiological features specific to MAP, with the latter showing a negative correlation with positive symptom severity.

In contrast to the previous findings indicating that MA dependence is associated with reductions in grey matter volumes in various brain areas, some studies have also reported increases in grey matter volumes. For example, Chang et al. (2005) showed that striatal structures, such as the putamen and globus pallidus, were enlarged in MA-dependent individuals; and Jernigan et al. (2005) reported volume increases in the parietal cortex, caudate nucleus, lenticular nucleus, and NAc, which is critically involved in reward states. In both studies, greater striatal volumes were not associated with cognitive impairment observed in the MA-dependent individuals. However, the findings of an enlarged NAc and putamen were replicated in a recent study by Jan et al. (2012), which also reported that increased volume in the right putamen was associated with better performance in a response inhibition task. It has therefore been hypothesized that these striatal volume increases may represent a compensatory response to maintain function, attributable to glial activation, neurite growth, and inflammatory changes (Chang et al., 2005; Jan et al., 2012; Jernigan et al., 2005), previously associated with MA-induced injury (Sekine et al., 2008). However, other studies did not observe striatal volumetric changes in MA-dependent participants (Kim et al., 2006; Schwartz et al., 2010). Such diverse findings highlight the need for more research, preferably longitudinal studies, to elucidate the causal relationship between MA use and structural brain changes, as well as between abstinence from the drug and brain recovery.

Adaptive glial changes have also been suggested to underlie observed white matter hypertrophy, which was detected in the temporal areas and occipital lobe in MA-dependent individuals (Thompson et al., 2004). Increases in white matter volume were also observed in the mid-posterior corpus callosum (pivotal for the interhemispheric transfer of information) in female MA-dependent individuals relative to corresponding healthy controls, while males exhibited slightly smaller volumes in this structure (Chang et al., 2005). Without having detected any size differences in the corpus callosum, Oh et al. (2005) reported changes in shape (including curvature and width) in MA-dependent individuals. Further macrostructural white matter changes have been detected in higher frequencies of frontal white matter hyperintensities (Alaee et al., 2014; Bae et al., 2006), and such white matter lesions are thought to be related to cerebral diffusion deficits, which have previously been observed in MA-dependent individuals (Chang et al., 2002).

Advanced neuroimaging techniques, such as DTI, further allowed the assessment of microstructural whiter matter integrity. Most frequently reported in DTI studies, fractional anisotropy (FA) represents a measure to which extent water diffusion in the brain is directional, detecting axon disorganisation and damage to myelination (Le Bihan et al., 2001). Several DTI studies reported reduced FA in frontal white matter in MA-dependent individuals (Chung et al., 2007; Salo et al., 2008; Tobias et al., 2010), which correlated with poor executive functioning (Chung et al., 2007). In addition, diminished microstructure in the genu (anterior end) of the corpus callosum was associated with impaired executive functioning (Kim et al., 2009) and cognitive control (Salo et al., 2009). These findings support the view that structural changes in frontal areas of the brain, including reduced white matter integrity, may underlie the cognitive impairments observed in MA-dependent individuals, which endure even after periods of abstinence (Berman et al., 2008). The first study to assess white matter integrity in the basal ganglia of MA-dependent individuals found higher diffusion in the left caudate and bilateral putamen (Alicta et al., 2009). As the apparent diffusion coefficient describes the mobility of water molecules in the brain (Le Bihan et al., 2001), the authors suggested that less myelination or greater inflammation may be the underlying pathophysiological processes; thereby supporting the argumentation from MRI studies described earlier.

No assessment of white matter structure has been conducted in MAP to date; nonetheless, Tobias et al. (2010) have previously investigated the relationship of white matter abnormalities in MA-dependent individuals with generalised psychiatric and depressive symptoms. Higher scores of both self-report scales correlated with higher FA in the left midcaudal superior corona radiata, however, the causal factors behind this counter-intuitive result are still to be elucidated, while the authors suggest that symptom awareness may be a modulating factor.

In sum, research findings from structural grey and white matter assessments in MA-dependent individuals have demonstrated diminished integrity in brain regions thought to underlie addictive behaviour, such as the NAc, OFC, and the limbic cortex, and have shown that damage, to the frontal brain in particular, may result in cognitive impairment. Additionally, there is emerging evidence that regions implicated in emotion regulation and social cognition, including the dorsolateral and ventrolateral PFC, the ACC, superior temporal gyrus, and insula (Davidson et al., 2000; Kohn et al., 2014), are affected by MA, potentially contributing to the inability to regulate emotions and consequent behavioural deficits.

As previously discussed, several lines of evidence demonstrate that MA abusers show socially problematic behaviours most likely linked to deficits in affect dysregulation (Homer et al., 2008). Even though data on the association with MA-related structural changes are scarce, there are a number of fMRI studies that have investigated functional brain deficits underlying impaired affect regulation and socio-emotional processing in MA dependence. Deficient neural activation in the bilateral insula and dorsolateral PFC has been shown in MA-dependent individuals relative to healthy controls when performing an emotion matching task with threatening or fearful visual scenes (Kim et al., 2011b). Employing a similar task using fearful and angry facial stimuli, Payer et al. (2008) reported a hypoactivation in the ventrolateral PFC, temporoparietal junction, and superior temporal sulcus in MA-dependent individuals, while amygdala activity was comparable to that in healthy controls. The functional deficits in the insula, PFC, and the temporal regions have been suggested to compromise empathy and social cognition in MA-dependent individuals (Kim et al., 2011b; Payer et al., 2008). Further findings of hypoactivations of the orbitofrontal cortex, temporal poles, and hippocampus during the performance of an empathy task support this notion of impaired empathic response and subsequent deficits in social functioning (Kim et al., 2010).

In a study by Payer et al. (2011) MA-dependent individuals demonstrated higher self-report and behavioural aggression, in addition to higher levels of self-report alexithymia (the difficulty to indentify and describe feelings). However, during an affect labelling task, MA participants showed similar PFC and amygdala activity, compared to healthy controls. Only during the emotion matching condition, did the authors find bilateral PFC hypoactivation. Based on these findings it has been suggested that in MA dependence, the aberrant expression of aggression may be attributable to lower emotional awareness, as indicated by decreased PFC activity during the processing of socio-emotional relevant stimuli. However, as the structural and functional deficits underpinning the MA-related impairment in affect regulation have not been elicited yet (Payer et al., 2011; Tabibnia et al., 2011), further research in this field is warranted.

In summary, research in MA dependence has highlighted behavioural, cognitive, and affective deficits with some corresponding functional and structural abnormalities in cortical and subcortical brain regions, particularly in the PFC and striatum. However, there is a shortage of data on how affective processes and the regulation thereof are compromised, and how these deficits directly relate to brain abnormalities in MA dependence and more importantly, in MAP. As the combination of psychotic symptoms, deficits in affect regulation, and cognitive impairment presents a significant challenge, the effectiveness of treatment may be particularly limited in MAP. Therefore, more research is needed for a better understanding of the neural mechanisms underlying the affective pathology in MA dependence and MAP. With this objective, the research project presented in the following chapters, has integrated several neuroimaging techniques to assess MA-related changes in brain structure and function and their relationship to impaired affect regulation. But first, we delineate the extent to which emotion regulation and social cognition capacities are impaired in MA dependence and MAP.

Chapter 3

Study 1: Social cognition and aggressive behaviour in methamphetamine dependence with and without a history of psychosis

As the literature review of the previous chapter highlighted, MA dependence can have detrimental on mental health, behaviour and social cognitive functioning. Social cognition skills, such as recognising facial expressions and inferring mental states of others, are essential for understanding behaviour of others, regulating one's own emotional state in the social context, and adapting behavioural responses. In substance abuse and psychotic disorders, deficits in social cognition may be related to impaired abilities to regulate emotions, which in turn may manifest in depressive symptoms, aggressive behaviour, and interpersonal violence. In this chapter we investigate social cognitive functioning and affect regulation as well as their association in individuals with MA dependence and MAP.

3.1. Introduction

The increasing prevalence of MA abuse and dependence has become a growing public health concern, given its devastating effect on users and on their communities (Watt et al., 2014). Problematic use of MA causes potentially long-lasting neurological damage (Krasnova & Cadet, 2009) and associated disruptions to cognitive-affective processes in humans (Kim et al., 2011a). Moreover, in addition to high levels of aggression and psychiatric symptoms, like depression, anxiety and psychotic symptoms (Payer et al., 2011; Plüddemann et al., 2010; Zweben et al., 2004), there is evidence that MA abuse has profound consequences on social-cognitive functioning, with resulting impoverishment of interpersonal interactions, as seen in animals and humans (Clemens et al., 2004; Homer et al., 2008). Although social-cognitive difficulties have previously been explored in substance use disorders, including those who use MA (Henry et al., 2009; Kim et al., 2011a), and psychotic disorders, such as schizophrenia and bipolar disorder (Rowland et al., 2013), relatively little is known about the association between deficits in social cognition and affect regulation in MA dependence and MAP.

Impaired abilities to regulate emotional responses have previously been linked to aggressive behaviour, depressive symptoms, and drug addiction (Bradley et al., 2011). Indeed, these pathologies are likely to share some underlying perturbations in dopaminergic and serotonergic pathways, comprising the anterior cingulate, orbitofrontal and medial prefrontal cortex, the ventral striatum and amygdala (Davidson et al., 2000; Goldstein & Volkow, 2011). The neurotoxic effects of MA, including damage to dopamine and serotonin axons, have consistently been shown to induce a variety of neuropathological changes in the brain (Barr et al., 2006; Krasnova & Cadet, 2009). This concurs with reported structural and functional alterations in the corticolimbic and corticostriatal pathways in MA dependence and MAP, changes that have been linked to abnormal emotional response, cognitive control, as well as psychosis (Aoki et al., 2013; London et al., 2004; Orikabe et al., 2011; Schwartz et al., 2010; Sekine et al., 2001, 2003, 2006).

Evidence from neuroimaging studies suggests that the fronto-limbic and fronto-striatal networks of the brain, demonstrated to be impaired in MA dependence (Baicy & London, 2007; London et al., 2014), may also play a key role in the neurobiology of social cognition (Carrington & Bailey, 2009; Fusar-Poli et al., 2009). Two core components of social cognition are Theory of Mind (ToM) and emotion recognition. While emotion recognition is the ability to infer an emotional state of another person, ToM relates to the ability to attribute beliefs, desires and intentions to oneself and others (Premack & Woodruff, 1978). A few studies have assessed emotion recognition and ToM abilities in MA abuse, demonstrating significant deficits in both domains in short-term as well as long-term abstinent individuals (Henry et al., 2009; Kim et al., 2011a). Similarly, diminished social cognition functioning, described in psychotic disorders such as bipolar disorder and schizophrenia (Bora et al., 2009; Fett et al., 2011; Rowland et al., 2013; Scholten et al., 2005) suggests that not only may these effects be apparent in MAP, but they may even be amplified. Nevertheless, to the best of our knowledge, no research on social cognition or on the interaction of emotion regulation and recognition has been conducted with MAP to date.

Accordingly, the purpose of this study was to test the hypothesis that MA dependence and MAP will be associated with deficits in emotion regulation and social cognition. Emotion regulation was operationalized in terms of self-report aggressive and depressive symptoms. Social cognition was tested using an archetypal ToM task, the Reading the Mind in the Eyes task, in addition to a sensitive emotion recognition task. We hypothesized that study groups with MA dependence and MAP relative to healthy controls would demonstrate higher levels of self-report aggression and depressive symptoms, along with compromised performance in the tasks of social cognition. We predicted that MAP patients would demonstrate greater impairment compared to MA-dependent participants. Finally, we tested the hypothesis that difficulties in social cognition would be linked to affect dysregulation.

3.2. Methods

3.2.1. Participants

Three groups were studied: 21 participants with MA dependence (MA group), 20 participants with MA dependence and a history of MA-associated psychosis (MAP group), and 21 healthy controls (CTRL group). Participants were recruited from drug rehabilitation facilities, hospitals and communities in Cape Town. The control participants were recruited from the same communities as individuals with MA dependence via advertising with flyers as well as word of mouth. All participants underwent a structured clinical interview for DSM-IV Axis I disorders (SCID-I) (First et al., 2002). Positive and negative symptoms within the MAP patients were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Participants were excluded from the study if they presented with: 1) additional substance dependencies other than nicotine for the MA and MAP groups, and any substance dependence in the control group; 2) lifetime and current diagnosis of any psychiatric disorders (other than MAP in the MAP group; 3) a history of psychosis prior to MA abuse; 4) a medical or neurological illness or head trauma; 5) a seropositive test for HIV. All participants in the MAP group were on treatment with neuroleptic medication, but treatment longer than twelve weeks was an additional exclusion criterion for the MAP group.

3.2.2. Emotion Recognition Task (ERT)

A modified version of the computerised emotion recognition task developed by Montagne et al. (2007) was used, in which participants were presented with the image of a face on a computer screen in front of them (Figure 3.1). On pressing the enter key the face morphed from the initial neutral expression into one of four emotional expression (angry, happy, sad, or fearful). The final image reached one of nine intensity levels of emotional expression (20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%). Participants were instructed to identify the emotion most strongly associated with each of the facial images presented in the morphing sequence. One of four emotion labels displayed underneath each face could be chosen by pressing the corresponding button on the keyboard. There was no time limit imposed for the response and the next trial began following the participant's response. Blocks of trials were presented in a fixed order in increasing intensity, with four trials of each emotion per intensity level (resulting in a total of 144 trials). Within each intensity block the emotions were presented in random order. Before the task started each participant was given four practice trials.

The facial stimuli consisted of grey-scale images of the faces of two male and two female actors taken from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998) and the Pictures of Facial Affect (Ekman & Friesen, 1976). The images were morphed from neutral to the desired intensity level in increments with two percent, with these gradations in intensity created with the WinMorph software (http://www.debugmode.com/winmorph/), and presented in E-Prime®1.2 (Psychology Software tools Inc., 2002). In various clinical samples, this task has been shown to detect selective impairments of emotion recognition according to the underlying neuropathology (Montagne et al., 2007).

Two participants in the MAP group did not complete the task and were therefore excluded from the data set.

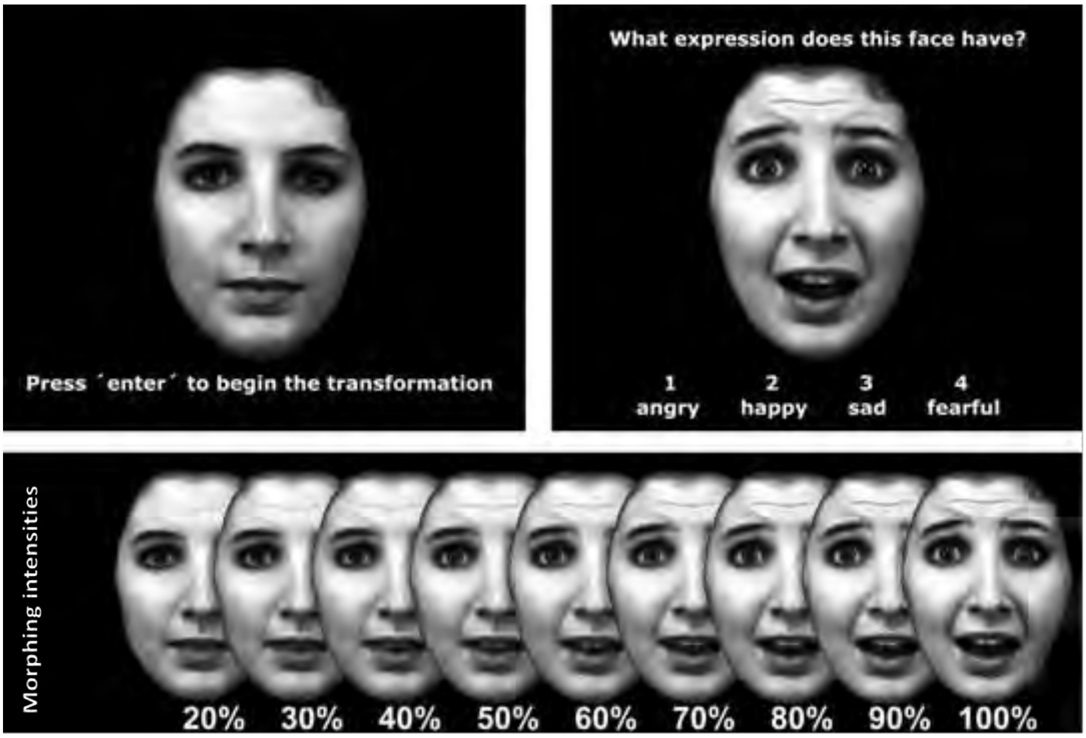


Figure 3.1. Example stimulus of the emotion recognition task, with start and end screen and the nine morph-intensities for dynamic display

3.2.3. Reading the mind in the eyes task (RMET)

The revised version of the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001) comprises 37 images (including 1 practice trial) of the eye region of the human face. Participants were asked to identify the state of mind of the person in the picture by choosing one of four mental state descriptors displayed around each image. Participants also received a list of descriptions of 93 different mental states (e.g. reflective, offended) to consult and there was no time limit for the task. Since the displayed emotions are complex and participants are supposed to detect what the person is feeling or thinking only from the eyes region, this task is considered an advanced ToM test.

3.2.4. Self-report questionnaires

The Buss & Perry Aggression Questionnaire (AQ) (Buss & Perry, 1992), a 29-item questionnaire that consists of four subscales: Physical Aggression, Verbal Aggression, Anger and Hostility, and a total score, was used to measure trait aggression.

The revised version of the Beck Depression Inventory (BDI-II) (Beck et al., 1996), a 21-item multiple-choice inventory, was used to assess depressive symptoms experienced two weeks previous to the testing session.

3.2.5. Data analysis

Statistical analyses were performed using IBM SPSS, version 21 (Armonk, NY: IBM Corp.), except for emotion recognition task analyses, which were performed in Stata/MP version 12. The assumption of normality of variables was assessed with the Shapiro-Wilk test. The study groups (MA, MAP, and CTRL) were compared in demographic and drug use measures using Kruskal-Wallis, Mann-Whitney-U, and chi-square tests as appropriate. Evidence for a main effect of group on aggression scores from a multivariate analysis of variance was followed by separate analyses for all four subscales and total scale. Finally, Sidak corrected *post hoc* pairwise comparisons were used to determine between-group differences in aggression subscores. Performances on the RMET and BDI questionnaire were compared using the Kruskal-Wallis and Mann-Whitney-U tests, as assumptions for parametric testing were violated. For all analyses *p*-values of < .05 were considered statistically significant.

Data from the ERT were analysed using logistic Generalised Estimating Equations (GEE) modelling. GEE allowed us to account for repeated measurements per participant and thereby control for introduced common variance. First, we tested overall main effects of group, emotion, and morphing level. Then, separate GEE models were fitted for each emotion. A final model included gender, BDI scores and a term representing the interaction term between morphing level and group. Again, separate models were fitted for each emotion. Interaction terms between morphing level and emotion as well as between BDI and group were non-significant and therefore, were omitted from the model.

Also, possible influences of MA measures (duration of use, duration of abstinence, and age of onset) on ERT and RMET were investigated. The effects of medication duration with antipsychotics and psychotic symptoms (PANSS scores) were also ascertained for the MAP group. Additionally, we explored the association between social cognition and emotion regulation abilities. These relationships were determined using the Spearman's rank correlation coefficient (r_s). The Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to correct for multiple testing.

3.3. Results

3.3.1. Demographics and Substance Use

Demographic and clinical characteristics of the three study groups are summarized in Table 3.1. Statistical analysis revealed no significant differences between groups in age and gender distribution. However, CTRLs had significantly higher levels of education compared to the MA group, $U = 127.5$, $p < .05$, and MAP group, $U = 46.5$, $p < .001$. Both clinical groups did not differ in MA use variables (i.e. duration, onset of use, and abstinence) or in non-MA drug use. However, both MA, $\chi^2(1) = 5.46$, $p < .05$, and MAP groups, $\chi^2(1) = 7.84$, $p < .05$, smoked significantly more in the last year than CTRLs. In addition, the MAP group used significantly more methaqualone in the last year relative to the CTRL group, $\chi^2(1) = 13.07$, $p < .001$.

Table 3.1. Demographic and clinical information for MA-dependent individuals with and without a history of psychosis and healthy controls

Demographic Measures	MA n=21	MAP n=20	CTRL n=21	test for group difference
male/female, n	17/4	16/4	17/4	$\chi^2(2)=.008$, $p=.996$
Age in years, median (range)	25 (19-30)	22 (18-41)	24 (18-38)	$H(2)=.487$, $p=.784$
Level Of Education in years, median (range)	10 (8-15)	10 (6-13)	12 (9-14)	$H(2)=17.693$, $p<.001$
Tobacco smokers in last year, n	18	18	11	$\chi^2(2)=9.604$, $p=.008$
Alcohol consumers in last year, n	14	16	11	$\chi^2(2)=3.493$, $p=.174$
Cannabis users in last year, n	12	16	10	$\chi^2(2)=4.757$, $p=.093$
Methaqualone users in last year, n	6	11	1	$\chi^2(2)=12.552$, $p=.002$
MA Use Measures				
Age at first use in years, median (range)	18 (12-27)	17 (12-40)		$U=198.0$, $p=.753$
Duration in years, median (range)	5 (1.5-10)	4.5 (1-9)		$U=188.5$, $p=.571$
Abstinence in days, median (range)	21 (1-240)	45 (1-270)		$U=168.0$, $p=.272$
Clinical Measures				
Neuroleptic Medication in days, M±SD (range)		43.7±21.8 (14-85)		
PANSS negative symptoms, median (range)		9 (7-37)		
PANSS positive symptoms, median (range)		10 (7-24)		
PANSS total score, median (range)		41 (22-100)		

PANSS: Positive and Negative Syndrome Scale. M: mean, SD: standard deviation.

5.3.2. Behavioural Measures

Table 3.2 presents mean scores and group comparisons for the Reading the Mind in the Eyes task, BDI depression and the aggression questionnaire. Both MA-dependent groups performed poorly in the RMET relative to the CTRL participants. Additionally, performance decrements were significantly greater in MAP, compared to MA-dependent participants. Scores on depressive symptoms were higher in MA and MAP groups relative to CTRLs, but did not differ between the two MA-dependent groups. A similar pattern of effects was observed with respect to scores on the aggression questionnaire, with a main effect of group observed, Pillai's Trace = .456, $F(8,114) = 4.21$, $p = .001$. The MA group relative to CTRL group showed higher scores in total and physical aggression, anger and hostility. The MAP group relative to CTRL demonstrated significantly higher anger and hostility scores. There were no significant differences in aggression scores between MA and MAP.

Table 3.2. Mean scores and group comparisons for RMET, BDI and aggression questionnaire in MA-dependent individuals with and without a history of psychosis and healthy controls

									Group Comparisons								
	MA		MAP		CTRL		Group statistic		MA-CTRL			MAP-CTRL			MA-MAP		
	M ± SD		M ± SD		M ± SD		*H(2)*	*p*	*U*	$p^{\#}$	*d*	*U*	$p^{\#}$	*d*	*U*	$p^{\#}$	*d*
RME task	21.3	5.4	16.2	6.3	24.1	5.0	15.03	<.001	154.0	.047	-0.54	71.0	<.001	-1.39	112.0	.005	0.87
BDI	19.6	9.9	17.6	12.3	5.1	4.4	24.13	<.001	37.5	<.001	1.89	67.5	<.001	1.35	180.5	.224	0.18
Aggression Questionnaire							*F(2,59)*	*p*		*p*	*d*		*p*	*d*		*p*	*d*
Total	91.1	17.8	84.7	13.3	73.1	19.4	6.04	.004		.003	0.97		.098	0.34		.541	0.20
Physical aggression	27.2	6.9	24.5	5.4	21.8	7.5	3.48	.037		.032	0.70		.460	0.41		.507	0.44
Verbal aggression	16.6	3.6	14.9	4.0	15.7	3.4	1.13	.331		.836	0.26		.838	-0.22		.362	0.45
Anger	21.6	4.7	19.0	4.7	15.0	4.4	11.19	<.001		<.001	1.45		.019	0.88		.213	0.55
Hostility	25.8	5.5	26.3	5.3	20.6	7.0	5.67	.006		.020	0.83		.012	0.92		.994	-0.09

RME: Reading the Mind in the Eyes task. BDI: Beck Depression Inventory. M: mean, SD: standard deviation. $p^{\#}$ exact significance (1-tailed), Cohen's ***d***: effect size.

Table 3.3 illustrates the mean ERT accuracy of the three study groups for each emotion collated over all nine morphing levels. It also indicates the rate for each emotion at which participants have misclassified the target emotion in error trials. Performance accuracy was defined as the percentage of correct recognition of the four emotions at each intensity level.

From the GEE analyses, significant main effects on accuracy were revealed for the factors group (Wald's χ^2 = 47.74, p < .0001), emotion (Wald's χ^2 = 209.28, p < .0001), morphing level (Wald's χ^2 = 241.65, p < .0001), and the group*emotion interaction (Wald's χ^2= 26.52, p < .0001). GEE models for the separate emotions revealed that, compared to healthy controls, the MAP group showed difficulties in identifying each of the four emotions for a constant morphing level: anger (Wald's χ^2=28.065, p<.0001; odds-ratio=0.264), fear (Wald's χ^2=36.587, p<.0001; odds-ratio=0.142), sadness (Wald's χ^2=11.435, p=.001; odds-ratio=0.454) and happiness (Wald's χ^2=17.388, p<.0001; odds-ratio=0.137). In the MA group relative to CTRLs, impairment was found in the recognition of anger (Wald's χ^2=5.427, p=.02; odds-ratio=0.575), while MA individuals performed equally to controls for the other emotions.

The final model revealed no main effects for gender or BDI scores, but a significant group*morphing level interaction (Wald's χ^2= 9.49, p = .009). Figure 3.2 displays ERT performance for each emotion at each morphing levels in MA, MAP, and CTRL participants. Increased intensity of the emotions resulted in higher levels of recognition accuracy in each group. Yet, this improvement was less pronounced for MAP compared to CTRL in the recognition of anger and fear. For a one unit increase in the morphing level of angry faces, the increase in task accuracy was twice as large (3.4%) in the CTRL group compared to the MAP group (1.7%). For fearful faces, recognition improved in the MAP group by the same degree as for anger (1.7%) for each one unit increase in morphing level, and by 4.7% in the CTRL participants. These differences were not apparent in sadness or happiness recognition. No significant differences were found between the MA and CTRL groups in terms of the impact of morphing level on accuracy.

Table 3.3. Percentage of correct answers collapsed over all intensity levels and of misclassifications for MA-dependent individuals with and without a history of psychosis and healthy controls

		Response given			
Emotion displayed	Group	Anger	Fear	Happiness	Sadness
Anger	MA	75%	9%	3%	13%
	MAP	59%	12%	7%	21%
	CTRL	84%	8%	2%	7%
Fear	MA	6%	86%	4%	4%
	MAP	15%	58%	12%	15%
	CTRL	6%	90%	3%	2%
Happiness	MA	3%	1%	96%	1%
	MAP	6%	2%	88%	4%
	CTRL	1%	0%	98%	0%
Sadness	MA	5%	9%	11%	75%
	MAP	15%	14%	14%	57%
	CTRL	5%	12%	9%	74%

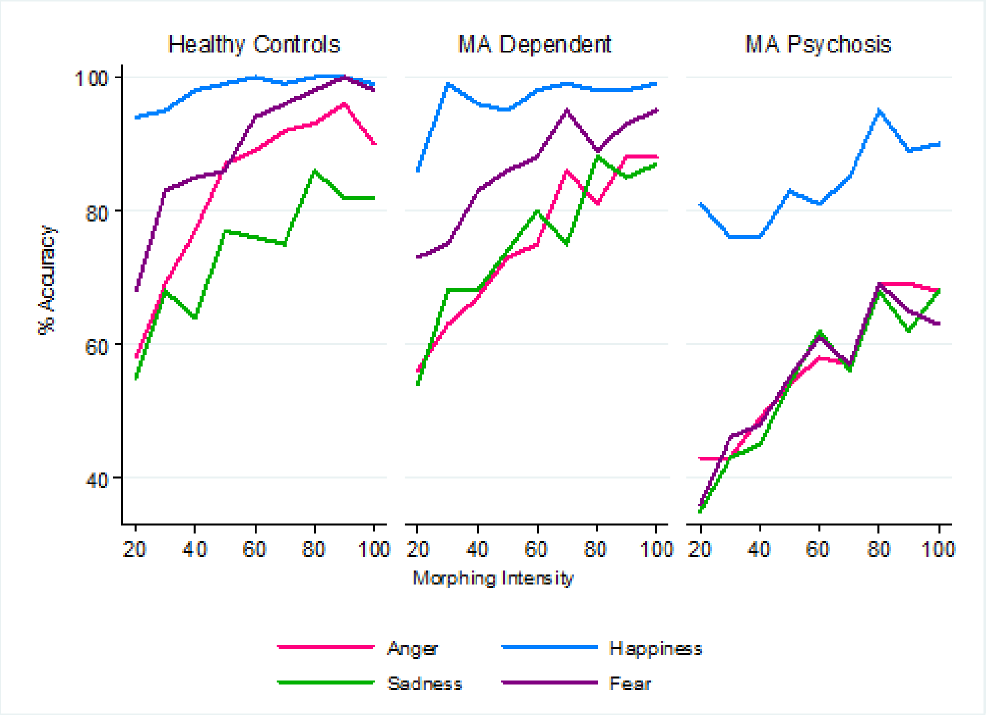


Figure 3.2. Percentage of accuracy in emotion recognition at each intensity level of morphed faces for all three study groups. Anger recognition was significantly reduced in MA-dependent group, whereas MAP patients display difficulties in recognition of all four emotions, compared to healthy controls.

To delineate the association between social cognition and emotion dysregulation and to investigate the influence of study group characteristics on these measures, a series of Spearman correlations was performed. There was no relationship between performance in the two social cognition tasks and aggression or BDI scores. Associations between duration of MA use and recognition accuracy for anger and total scores (negative in MA group and positive in MAP group) did not survive FDR correction. Performances on both tasks did not correlate with psychotic symptoms (PANSS) or medication duration in the MAP group.

3.4. Discussion

The present study examined social cognition functioning and emotion dysregulation in MA dependence and MA-associated psychosis and revealed the following main findings. Both MA and MAP group demonstrated impairment in affect regulation abilities in terms of self-report aggressive and depressive symptoms, with no statistical significant differences between the two groups. The two MA-dependent groups also showed diminished social cognition skills in terms of facial emotion recognition and theory of mind, with MAP participants demonstrating greater impairment compared to the MA group.

In agreement with previous research in MA dependence (Payer et al., 2011; Plüddemann et al., 2010; Sekine et al., 2006; Semple et al., 2005), both clinical groups reported increased aggression and depressive symptoms. Such behavioural and affective changes may impact entire communities by leading to negative social outcomes like social withdrawal/rejection or increased rates of crime, including physical and sexual violence (Sommers & Baskin, 2006; Watt et al., 2014). As emerging evidence from studies in MA abuse (Sekine et al., 2006), impulsive aggression (Frankle et al., 2005), and psychiatric patients (van Praag et al., 1990) has shown, deficient serotonergic neurotransmission, especially in the neural circuitry of emotion regulation, may play a role in underpinning increased aggressive behaviour.

Previous studies have further suggested a mediating effect of positive psychotic symptoms (hallucinations, suspiciousness, and delusional beliefs) and impulsivity on the association between MA abuse and hostility (Lapworth et al., 2009). In the present study, however, we did not detect a relationship between psychotic symptoms and aggression subscales in MAP patients. A possible confound in the MAP patients may have been the effect of antipsychotic medication in reducing aggression symptom severity. Indeed, MAP patients only scored higher in the anger and hostility subscales, while the MA group additionally showed higher scores in total and physical aggression, compared to healthy controls. But since almost all MAP participants were receiving antipsychotic medications at the time of the study, it was not possible to test this hypothesis.

In addition to these impaired abilities in affect regulation, both MA-dependent groups demonstrated decreased social cognitive functioning in terms of poor REMT performance. This is consistent with previous research in MA abusers showing reduced abilities to attribute mental states to others (Henry et al., 2009; Kim et al., 2011a) and to demonstrate empathic response to others during social interaction (Kim et al., 2010). However, to our best knowledge this is the first study to assess social cognition in patients with MAP.

Social cognition was more impaired in MA-dependent patients with a history of psychosis than those who did not manifest psychotic symptoms. MA and MAP participants were comparable with respect to MA use variables, indicating that the greater impairment in social cognition was not due to more severe MA dependence in the MAP subjects. Instead, the greater deficits observed in the MAP group may represent an additive consequence of the effects of MA abuse on social cognition reviewed above, and the confirmed association of other psychotic disorders, including schizophrenia, bipolar disorder and affective psychoses with ToM impairment (Bora et al., 2009; Rowland et al., 2013). Structural and dopaminergic brain abnormalities associated with psychotic symptoms in MA users that may underlie deficits in social cognition include reduced dopamine receptor density in the striatum, the orbitofrontal and dorsolateral prefrontal cortex (Sekine et al., 2001; 2003), and structural grey matter abnormalities in the amygdala, hippocampus, inferior frontal gyrus, frontopolar cortex, and superior temporal gyrus (Aoki et al., 2013; Orikabe et al., 2011). While lesions to the amygdala and orbitofrontal cortex have been linked to impaired facial emotion recognition (Adolphs, 2002); it is superior temporal gyrus alterations that seem to reflect deficits in face processing in general (Haxby et al., 2000).

In this study chronic MA use was associated with impairments in the recognition of other people’s emotions, and once again this effect was most apparent in the MAP group. Of the four emotions tested, anger was the only emotion in which both MA-dependent groups demonstrated deficits relative to controls. This stands in contrast to findings reported in a previous study where MA abusers evidenced selective impairment in fear recognition (Kim et al., 2011a). However, impaired anger recognition has previously been identified in patients with damage to the ventral striatum (Calder et al., 2004) and in patients with frontotemporal lobar degeneration (Kessels et al., 2007). The role of the prefrontal cortex in the recognition of anger has further been supported by findings of transcranial magnetic stimulation induced processing disruptions in the medial prefrontal cortex leading to impaired processing of angry facial expressions (Harmer et al., 2001). In addition, increased activation in the orbitofrontal and anterior cingulate cortex was found when participants were shown facial expressions of anger (Blair et al., 1999). As these brain regions are part of the mesolimbic and mesocortical pathways, a dysfunction in the dopaminergic system may underlie the observed deficits in social cognition. Indeed, emerging evidence suggested that disruption in the dopamine system (by antagonist administration) leads to a selective impairment in the recognition of anger, while recognition of other emotions and faces remained unaffected (Lawrence et al., 2002). Tellingly, the same regions of the brain involved in the recognition of anger (medial orbitofrontal cortex, rostral anterior cingulate cortex, ventral striatum) form part of the reward circuitry in the brain demonstrated to be sensitive to the acute administration of MA in healthy drug-naive participants (Völlm et al., 2004). While short-term MA use does not necessarily lead to neurocognitive impairment, and may even prove beneficial (Hart et al., 2012), prolonged use likely leads to damage to these circuits, as demonstrated by metabolic and morphometric abnormalities in MA-dependent populations (Aoki et al., 2013; Chang et al., 2005; London et al., 2004; Nakama et al., 2011; Orikabe et al., 2011; Schwartz et al., 2010).

In contrast to the selective impairment in MA, MAP patients demonstrated difficulties in the recognition of all tested emotions (happiness, sadness, anger, and fear) relative to healthy controls. Additionally, MAP participants demonstrated reduced sensitivity to increases in the intensity of aversive emotions (fear, anger), implying even greater difficulties in the recognition of these two negative emotions. These results converge with findings of impaired facial affect recognition in other psychiatric disorders. Applying a similar emotion recognition morphing paradigm, a study by Scholten et al. (2005) showed that schizophrenia patients relative to healthy controls performed worse in recognising negative emotions, without having difficulties in recognising faces in general. However, the present study did not include a control test of face recognition; therefore, we cannot exclude the possibility of impaired face perception contributing to the broad deficits in emotion recognition in MAP.

We also aimed to assess the relationship between social cognition impairment and affect dysregulation in MA and MAP; however, the expected association could not be found. These data may suggest distinct underlying brain-network abnormalities for aggression and social cognition. Alternatively, they may reflect various limitations of our study design.

Several such limitations exist. First, nearly all MAP patients had received antipsychotic medication at the time of the study. While previous research found a mediating effect of neuroleptics on ToM and facial emotion recognition impairment in bipolar disorder patients (Martino et al., 2011), the present study did not find any influence of treatment duration on social cognition capacity in MAP. Second, the present study only included self-report measures of emotion regulation, potentially limiting the validity of the data. Finally, the cross-sectional nature of our data does not allow for statements regarding the causal effect of MA use on either social cognition or affect regulation. MA use variables correlated with behavioural measures only weakly, not surviving FDR correction. It is therefore difficult to assess how much of a contribution MA made to the deficits in social cognition and affect regulation in the two patient groups.

In summary, the present study demonstrated that emotion recognition and ToM abilities, which are critical in the context of social behaviour, are compromised in MA-dependent individuals, with even greater impairment in patients with MAP. In future, investigations of the association of social cognition and affect regulation in MA dependence and MAP may usefully include neuroimaging applications to disentangle possible underlying differences in brain network functioning.

Chapter 4

Study 2: Frontotemporal grey matter alterations and affect regulation in methamphetamine dependence with and without a history of psychosis

The previous chapter demonstrated how social cognition skills are impaired in individuals with MA dependence and MAP and to which extent these populations report increased levels of depressive symptoms ad aggressive behaviour. Recent neuroimaging studies suggested that structures in corticolimbic neural networks may be affected in MA and psychotic disorders (Baicy & London, 2007; Fusar-Poli et al., 2011), and although these abnormalities may in turn be associated with cognitive impairment and aggressive behaviour, their association with emotion dysregulation is less well studied. The current chapter investigates grey matter structure changes and how these abnormalities relate to affect dysregulation in MA dependence and MAP.

4.1. Introduction

While the initial effects of MA may include increased attention, self-confidence and feelings of euphoria (Meredith et al., 2005; Panenka et al., 2013), continued use of this psychostimulant may be far more noxious. Adverse affective symptoms such as depression, anxiety, and aggressive behavior (Lapworth et al., 2009; Plüddemann et al., 2010), as well as psychotic symptoms such as delusions and hallucinations (Barr et al., 2006; Meredith et al., 2005; Plüddemann et al., 2013; Zweben et al., 2004) have been reported in such cases. These effects are often severe and debilitating, and may persist long after cessation of drug use (Akiyama et al., 2011). However, despite the clinical and scientific importance of this field, current understandings of the neural mechanisms underlying affective symptomatology in MA dependence and MAP remain limited.

Both animal and human studies have emphasized the neurotoxic effects of MA on dopaminergic and serotonergic terminals (Davidson et al., 2001; Krasnova and Cadet, 2009; Reiner et al., 2009; Sato et al., 1992; Yamamoto et al., 2010). Magnetic resonance imaging (MRI) studies have supported these models by demonstrating heterogeneous morphological grey matter changes in MA abuse. To date, the most consistent changes have been reduced grey matter volumes in frontal lobe systems (Daumann et al., 2011; Kim et al., 2006; Nakama et al., 2011; Schwartz et al., 2010). Additional findings include volumetric loss in the insula (Schwartz et al., 2010), temporal cortex (Nakama et al., 2011), cingulate cortex and hippocampus (Thompson et al., 2004), and striatum and parietal cortex (Morales et al., 2012), as well as an increase in volumes in the striatum and parietal cortex (Chang et al., 2005; Jernigan et al., 2005). There is some evidence that such structural deficits may be associated with cognitive impairment (Berman et al., 2008; Kim et al., 2006; Scott et al., 2007; Thompson et al., 2004), but it is unclear whether they are also associated with emotion dysregulation.

Individuals with MAP may demonstrate specific cortical and subcortical deficits in structure and function (Sato et al., 1992). Such structural abnormalities have been reported in the amygdala and hippocampus (Orikabe et al., 2011) as well as in the inferior frontal gyrus, frontopolar cortex, and superior temporal gyrus (Aoki et al., 2013). Similar volumetric changes in the hippocampus and frontotemporal cortex have been described in a number of MRI studies of schizophrenia and individuals at risk for psychosis (Fusar-Poli et al., 2011; Wright et al., 2000). Nevertheless, relatively few clinical studies have specifically explored the associations of MAP with emotional dysregulation; and only one study to date has compared brain imaging in MAP and MA (Howells et al., 2014).

In order to examine and compare the changes in brain structure and emotion regulation in MA dependence and MAP, we tested three study groups: MA-dependent individuals with a history of psychosis; those without a history of psychosis; and healthy controls. Cortical thickness in frontotemporal brain areas was evaluated, and seven subcortical structures were selected for volumetric assessment. Included structures were the amygdala, hippocampus, nucleus accumbens, caudate, pallidum, putamen, and thalamus, as these are all either involved in emotion regulation or have been found to be altered in MA users. Scores of self-report questionnaires assessing affect regulation were recorded. It was hypothesized that both MA-dependent groups would display cortical thinning in frontotemporal regions and volumetric changes in subcortical structures, particularly in the basal ganglia. Further, we hypothesized that these effects would be associated with emotion dysregulation. Finally, we predicted that observed effects would be strongest in the MAP group.

4.2. Methods

4.2.1. Participants

Three groups were studied: 22 MAP patients, 21 participants with MA dependence and no psychosis (MA group), and 21 healthy controls (CTRL group). All participants were right-handed and matched for age and gender. Inhalation was the exclusive route of MA administration. Participants were recruited from drug rehabilitation facilities, hospitals and communities in Cape Town. Clinical assessment was carried out by trained staff of the Department of Psychiatry and Mental Health, University of Cape Town (UCT), using the SCID-I for DSM-IV-TR (First et al., 2002). Positive and negative symptoms within the MAP group were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Participants were excluded from the study if they presented with: 1) additional substance dependencies other than nicotine for the MA and MAP groups, and any substance dependence in the control group; 2) lifetime and current diagnosis of any psychiatric disorders (other than MA dependence and MAP in the MA and MAP groups); 3) a history of psychosis prior to MA abuse; 4) a medical or neurological illness or head trauma; 5) a seropositive test for HIV; 6) MRI incompatibilities or known claustrophobia. All participants in the MAP group were on treatment with neuroleptic medication. Treatment of longer than twelve weeks' duration at the time of scanning was an additional exclusion criterion for the MAP group.

4.2.2. MRI Acquisition and image processing

Imaging was performed at the Cape Universities Brain Imaging Centre (CUBIC) using a Siemens Magnetom Allegra 3T system. A high-resolution, T1-weighted, 3D-MEMPRAGE sequence (scan parameters: TR=2530ms; graded TE=1.53, 3.21, 4.89, 6.57ms; flip angle=7°; FOV=256mm) was used to produce 160 1-mm-thick sagittal images. For screening purposes, transversal T2-weighted images (TR=9000ms; TR=96ms; flip angle=180°; FOV=230mm; slice thickness=5mm) as well as fluid-attenuated inversion recovery (FLAIR) transversal images (TR=4200ms; TR=95ms; flip angle=150°; FOV=230mm; slice thickness=5mm) were obtained. An experienced radiologist, blind to diagnosis, examined each scan for structural abnormalities. This resulted in the exclusion of one participant from this study and other parts of the research project.

MRI scans were analyzed using the FreeSurfer software package v5.1 (http://surfer.nmr.mgh.harvard.edu/). Regional estimates of cortical thickness and subcortical volumes were assessed with a specialized surface-based reconstruction and automatic labelling tool. In summary, FreeSurfer processing includes motion correction, skull-stripping, Talairach transformation, segmentation of subcortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter/ white matter boundary, automated topology correction, and surface deformation. After a non-rigid registration to a spherical atlas the cerebral cortex is parcellated into 34 regions of interest in each hemisphere based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004). Cortical thickness is measured as the closest distance from the grey/white matter boundary to the grey matter/ cerebrospinal fluid boundary at each tesselation vertex.

Final images were visually inspected and manually corrected where necessary. Five participants were excluded due to gross motion artefacts and resultant poor image quality. Thus, the final MRI data set comprised scans of 59 study participants (21

MA, 19 MAP, and 19 CTRL). To quantify neuroanatomical alterations, we extracted mean cortical thickness and mean subcortical volume of specific structures of interest of all participants.

4.2.3. Affect regulation measures

The study employed the emotion reactivity scale (ERS) (Nock et al., 2008), a 21-item self-report tool assessing 1) sensitivity to emotional stimuli, 2) intensity of emotional experience, and 3) persistence of emotional experiences. Participants were asked to rate each item on a 5-point scale (from 0 = *not at all like me* to 4 = *completely like me*) according to their individual experience of emotions on a regular basis. Higher scores indicated higher levels of emotional reactivity.

Participant further completed the difficulties in emotion regulation scale (DERS) (Gratz & Roemer, 2004), a 36-item self-report measure. Subscales assessed six different dimensions: 1) lack of emotional awareness, 2) lack of emotional clarity, 3) difficulties engaging in goal-directed behaviour, 4) difficulties in impulse-control, 5) nonacceptance of emotional responses, and 6) limited access to emotion regulation strategies. Participants rated how often each item applied to them on a 5-point scale (from 1 = *almost never* to 5 = *almost always*). Higher total and subscale scores indicated greater difficulties in emotion regulation.

4.2.4. Statistical Analysis

Statistical analysis was performed using IBM SPSS 22 (Armonk, NY: IBM Corp). Assumption of normality of each variable was tested with the Shapiro-Wilk test. The study groups (MA, MAP, and CTRL) were compared across demographic and drug use variables using Kruskal-Wallis and chi-square tests as appropriate. For all analyses, *p*-values of < .05 were considered statistically significant.

A multivariate analysis of covariance (MANCOVA) with age as covariate was employed to assess group-level differences in cortical thickness in the 23 frontotemporal regions of interest, for each hemisphere separately. Significant main effects were followed up with univariate ANCOVAs and Sidak corrected pairwise comparisons, where applicable.

For each of the seven subcortical structures of interest a GLM was fit with age and intracranial volume as covariates and hemisphere as a within-factor. The Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to correct for multiple testing. Within structures that survived FDR adjustment, follow-up ANCOVAs and Sidak corrected pairwise comparisons were conducted.

Group differences in ERS and DERS total scores and subscales were assessed using non-parametric Kruskal-Wallis tests and follow-up Mann-Whitney tests (due to heterogeneity of variance in ERS and non-normality of DERS data in the CTRL group). Main tests and pairwise comparisons were FDR corrected in order to decrease the risk of type I error.

To explore the association of cortical mean thickness or subcortical mean volume of regions of interest with affect regulation measures we calculated parametric Pearson's correlation coefficient (r), or Kendall's tau-b (T) in cases where the assumption of normal distribution was violated. In addition, correlations between MRI data, MA measures (onset, duration, and abstinence) and clinical data were calculated. Analyses were restricted to areas with significant group differences and FDR-corrected for multiple comparisons.

4.3. Results

4.3.1. Demographics and Substance Use

There were no significant differences in age and gender distribution between the three study groups (Table 4.1). However, the control group had significantly higher levels of education compared to the MA, $U = 114.5$, $p = .019$, and MAP groups, $U = 39.0$, $p < .001$. Across both MA-dependent groups, participants did not differ in MA use variables (i.e. duration and onset of use, and duration of abstinence) or in non-MA drug use variables. However, controls smoked significantly less in the past year than either the MA group, $\chi^2(1) = 5.199$, p = .023, or the MAP group, $\chi^2(1) = 6.269$, *p* = .012. Further, the MAP group used significantly more methaqualone in the last year than did the controls, $\chi^2(1) = 10.364$, $p = .001$.

Table 4.1. Demographic and clinical information for MA-dependent individuals with and without a history of psychosis and healthy controls

Demographic Measures	MA n=21	MAP n=19	CTRL n=19	test for group difference
male/female, n	17/4	16/3	15/4	$\chi^2(2)=.177, p=.915$
Age in years, median (range)	25 (19-35)	23 (18-38)	23 (19-37)	$H(2)=.585, p=.746$
Level Of Education in years, median (range)	10 (8-15)	9.5 (8-13)	12 (9-14)	$H(2)=16.42, p<.001$
Tobacco smokers in last year, n	18	17	10	$\chi^2(2)=8.731, p<.05$
Alcohol consumers in last year, n	14	15	9	$\chi^2(2)=4.205, p=.122$
Cannabis users in last year, n	12	16	9	$\chi^2(2)=5.947, p=.051$
Methaqualone users in last year, n	6	10	1	$\chi^2(2)=6.654, p<.01$
MA Use Measures				
Age at first use in years, median (range)	18 (12-27)	17 (12-32)		$U=177, p=.540$
Duration in years, M±SD (range)	5.6±2.3 (1.5-10)	5.3±3 (1-12)		$t(38)=.333, p=.741$
Abstinence in days, median (range)	21 (1-240)	50 (1-270)		$U=161.5, p=.302$
Clinical Measures				
Neuroleptic Medication in days, M±SD (range)		45.3±21.4 (14-85)		
PANSS negative symptoms, median (range)		16 (7-37)		
PANSS positive symptoms, median (range)		10 (7-24)		
PANSS general psychopathy, median (range)		24 (16-46)		
PANSS total score, median (range)		52 (33-100)		

PANSS: Positive and Negative Syndrome Scale. M: mean, SD: standard deviation

4.3.2. MRI Measures

Cortical Findings

The GLM revealed a group effect on cortical thickness in the left hemisphere, $F(46,68) = 1.615$, $p = .036$. Table 4.2 presents specific cortical areas of the left frontal, temporal and insular lobe with group values of mean thickness in mm (adjusted for age) and percentage differences between groups. Cortical thickness in the MA group was significantly increased in the entorhinal as well as the insular cortex compared to healthy controls. The MAP group showed significant cortical thinning in the pars triangularis compared to healthy controls. The greatest differences in cortical thickness were found between the two MA-abusing groups, with the MAP group showing decreased thickness in the fusiform, inferior temporal, lateral and medial orbitofrontal, pars orbitalis and triangularis, and the insular cortex. Results remained the same when including gender as a covariate in the model. No group effect was found for cortical thickness of the right hemisphere, *F*(46,68) = 1.014, *p* = .473.

Table 4.2. Left hemisphere frontotemporal cortical thickness (mm) and group comparisons between MA-dependent individuals with and without a history of psychosis and healthy controls

		Mean cortical thickness							Group comparisons					
		MA		MAP		CTRL		group	MA-CTRL		MAP-CTRL		MA-MAP	
Cortical regions	Lobe	M ± SE		M ± SE		M ± SE		statistic	% diff.	*p*	% diff.	*p*	% diff.	*p*
Banks of sup.temp.sulcus	T	2.522	.034	2.450	.036	2.504	.036	1.102$^{n.s.}$	0.7	n.s.	-2.2	n.s.	2.9	n.s.
Caudal anterior cingulate	F	2.549	.037	2.463	.039	2.453	.039	1.934$^{n.s.}$	3.9	n.s.	0.4	n.s.	3.5	n.s.
Caudal middle frontal	F	2.644	.031	2.552	.033	2.600	.033	2.044$^{n.s.}$	1.7	n.s.	-1.8	n.s.	3.6	n.s.
Entorhinal	T	3.455	.056	3.320	.059	3.231	.059	3.920*	6.9	.023	2.8	n.s.	4.1	n.s.
Fusiform	T	2.669	.030	2.545	.031	2.591	.031	4.267*	3.0	n.s.	-1.8	n.s.	4.9	.017
Inferior temporal	T	2.741	.035	2.613	.036	2.653	.036	3.439*	3.3	n.s.	-1.5	n.s.	4.9	.040
Lateral orbitofrontal	F	2.751	.032	2.618	.034	2.696	.034	4.037*	2.0	n.s.	-2.9	n.s.	5.1	.019
Medial orbitofrontal	F	2.583	.028	2.462	.029	2.511	.029	4.594*	2.9	n.s.	-2.0	n.s.	4.9	.012
Middle temporal	T	2.886	.028	2.792	.030	2.835	.030	2.684$^{n.s.}$	1.8	n.s.	-1.5	n.s.	3.4	n.s.
Parahippocampal	T	2.708	.045	2.656	.048	2.677	.048	0.325$^{n.s.}$	1.2	n.s.	-0.8	n.s.	2.0	n.s.
Paracentral	F	2.484	.037	2.408	.039	2.419	.039	1.183$^{n.s.}$	2.7	n.s.	-0.5	n.s.	3.2	n.s.
Pars opercularis	F	2.679	.030	2.600	.032	2.674	.032	1.965$^{n.s.}$	0.2	n.s.	-2.8	n.s.	3.0	n.s.
Pars orbitalis	F	2.777	.045	2.600	.047	2.747	.047	4.100*	1.1	n.s.	-5.4	n.s.	6.8	.027
Pars triangularis	F	2.605	.028	2.491	.029	2.631	.029	6.617**	-1.0	n.s.	-5.3	.004	4.6	.018
Precentral	F	2.570	.034	2.517	.035	2.538	.035	0.593$^{n.s.}$	1.3	n.s.	-0.8	n.s.	2.1	n.s.
Rostral anterior cingulate	F	2.725	.041	2.751	.043	2.660	.043	1.219$^{n.s.}$	2.4	n.s.	3.4	n.s.	-0.9	n.s.
Rostral middle frontal	F	2.460	.024	2.409	.026	2.404	.026	1.576$^{n.s.}$	2.3	n.s.	0.2	n.s.	2.1	n.s.
Superior frontal	F	2.861	.034	2.775	.035	2.802	.035	1.656$^{n.s.}$	2.1	n.s.	-1.0	n.s.	3.1	n.s.
Superior temporal	T	2.808	.032	2.755	.034	2.814	.034	0.926$^{n.s.}$	-0.2	n.s.	-2.1	n.s.	1.9	n.s.
Frontal pole	F	2.827	.055	2.836	.058	2.752	.058	0.632$^{n.s.}$	2.7	n.s.	3.1	n.s.	-0.3	n.s.
Temporal pole	T	3.693	.057	3.598	.060	3.749	.060	1.602$^{n.s.}$	-1.5	n.s.	-4.0	n.s.	2.6	n.s.
Transverse temporal	T	2.413	.052	2.297	.054	2.336	.060	1.243$^{n.s.}$	3.3	n.s.	-1.7	n.s.	5.1	n.s.
Insula	I	3.000	.032	2.870	.034	2.868	.034	5.384**	4.6	.019	0.1	n.s.	4.5	.021

Cortical thickness means adjusted for age. Anatomical areas defined in FreeSurfer according to the Desikan atlas. Pairwise comparisons are Sidak-corrected for multiple comparisons. Group statistic based on ANCOVAs, *F*(2,55) following a statistical significant omnibus test for left hemisphere only.**p*<.05, ***p*<.001, n.s.-non-significant. Multivariate test for right hemisphere cortical thickness differences was not statistically significant. Lobe: F-frontal, T-temporal, I-insular. M: mean, SE: standard error.

Subcortical Findings

Table 4.3 shows subcortical regions of interest with group differences in mean volumes in mm^3 (adjusted for age and intracranial volume). Of the seven regions assessed bilaterally only the hippocampus volume showed an effect of group, $F(4,108) = 3.774$, $p = .007$. There was a significant volume reduction in the left hippocampus of the MAP group compared to both the MA and CTRL groups. The right hippocampus volume was significantly smaller in the MAP group than in the MA group. Results did not change when controlling for gender in the model.

Table 4.3. Volumetric measures (mm^3) of subcortical structures and group comparisons between MA-dependent individuals with and without a history of psychosis and healthy controls

		Mean subcortical volume						Group comparisons					
Subcortical		MA		MAP		CTRL		MA-CTRL		MAP-CTRL		MA-MAP	
structure	Hemisphere	M ± SE		M ± SE		M ± SE		% diff.	*p*	% diff.	*p*	% diff.	*p*
Amygdala	L	1628.3	30.9	1555.2	32.5	1610.2	32.6	1.1	n.s.	-3.4	n.s.	4.7	n.s.
	R	1676.5	32.3	1671.7	34.0	1697.0	34.1	-1.2	n.s.	-1.5	n.s.	0.3	n.s.
Hippocampus	L	3852.6	66.2	3510.1	69.6	3798.1	69.9	1.4	n.s.	-7.6	.016	9.8	.002
	R	4011.9	67.3	3682.3	70.7	3879.3	71.0	3.4	n.s.	-5.1	n.s.	9.0	.004
Nucleus accumbens	L	697.7	22.4	717.7	23.6	675.1	23.7	3.3	n.s.	6.3	n.s.	-2.8	n.s.
	R	705.5	26.1	728.3	27.4	677.8	27.5	4.1	n.s.	7.5	n.s.	-3.1	n.s.
Caudate	L	3942.7	81.4	3928.5	85.7	3987.6	86.0	-1.1	n.s.	-1.5	n.s.	0.4	n.s.
	R	4093.3	79.6	4135.9	83.7	4129.4	84.1	-0.9	n.s.	0.2	n.s.	-1.0	n.s.
Pallidum	L	2052.6	52.8	2116.4	55.6	2022.6	55.8	1.5	n.s.	4.6	n.s.	-3.0	n.s.
	R	1857.2	51.2	1861.4	53.9	1770.2	54.1	4.9	n.s.	5.1	n.s.	-0.2	n.s.
Putamen	L	6480.4	155.5	6604.4	163.6	6380.5	164.2	1.6	n.s.	3.5	n.s.	-1.9	n.s.
	R	6193.9	145.0	6454.7	152.5	6124.0	153.2	1.1	n.s.	5.4	n.s.	-4.0	n.s.
Thalamus	L	7392.0	155.9	7240.2	164.0	7209.0	164.7	2.5	n.s.	0.4	n.s.	2.1	n.s.
	R	7704.8	161.1	7515.6	169.5	7472.1	170.2	3.1	n.s.	0.6	n.s.	2.5	n.s.

Subcortical volume means (M) adjusted for age and intracranial volume and Standard Error (SE). Anatomical areas defined in FreeSurfer according to the Desikan atlas. Pairwise comparisons are Sidak-corrected for multiple comparisons. Hemisphere: L-left, R-right.

4.3.3. Affect Regulation Measures

ERS and DERS mean scores with standard deviations, test results and effect size for group differences can be seen in Table 4.4. Both MA-dependent groups showed significantly higher scores in total ERS (indicating decreased emotion regulation) and in all three ERS subscales. Further, both MA-dependent groups scored significantly higher in total DERS than did healthy controls, with the MAP group showing impairments in all dimensions, barring emotional awareness. The MA group only reported difficulties relating to understanding emotions and impulse control.

Table 4.4. Mean scores and group comparisons for DERS and ERS questionnaires in MA-dependent individuals with and without a history of psychosis and healthy controls

	Mean scores							Group comparisons								
	MA		MAP		CTRL		group statistic *H*(2)	MA-CTRL			MAP-CTRL			MA-MAP		
	Mean ±	SD	Mean ±	SD	Mean ±	SD		*U*	*p*	*d*	*U*	*p*	*d*	*U*	*p*	*d*
ERS total	29.81	19.87	31.74	16.26	16.29	9.76	10.740**	133.5	.028	0.86	98.0	<.001	1.15	231.5	n.s.	-0.11
Intensity	10.95	7.23	12.48	6.20	6.33	4.47	10.536**	140.0	.042	0.77	97.5	.001	1.14	220.5	n.s.	-0.23
Persistence	5.71	4.42	5.35	3.94	2.67	2.27	7.624*	135.5	.030	0.87	131.5	.008	0.83	228.0	n.s.	0.09
Sensitivity	13.14	9.38	13.91	8.54	7.29	4.76	7.928*	140.5	.044	0.79	123.0	.005	0.96	231.5	n.s.	-0.09
DERS total	82.71	18.04	88.50	20.85	67.43	17.84	11.379**	119.5	.012	0.85	104.0	.001	1.09	189.0	n.s.	-0.30
Awareness	17.10	3.89	15.91	4.56	14.76	4.23	2.726$^{n.s.}$									
Clarity	10.86	3.77	12.32	4.37	8.43	3.16	9.542**	137.0	.033	0.70	109.5	.003	1.02	190.0	n.s.	-0.36
Goals	12.71	4.42	13.82	4.08	10.38	4.13	7.320*	149.5	n.s.	0.54	125.5	.010	0.84	188.5	n.s.	-0.26
Impulse	13.76	4.87	13.23	4.65	9.81	4.86	12.101**	101.0	.002	0.81	109.0	.003	0.72	213.5	n.s.	0.11
Nonacceptance	11.38	4.26	13.91	4.37	10.67	3.80	5.962*	205.5	n.s.	0.18	134.0	.016	0.79	159.0	n.s.	-0.59
Strategies	16.90	5.97	19.32	6.11	13.38	3.97	10.503**	146.0	n.s.	0.69	99.5	.001	1.15	176.0	n.s.	-0.40

Mean (M) and Standard Deviation (SD) of ERS and DERS scores. All statistical tests were adjusted for False Discovery Rate. *p<0.05, **p<0.01, n.s.-non-significant. ERS: Emotion Reactivity Scale, DERS: Difficulties in Emotion Regulation Scale. Cohen's *d*: effect size.

4.3.4. Correlations

In cases where cortical thickness differed significantly between groups, associations with emotional dysregulation were calculated in MA abusing groups (Table 4.5). Significant associations of reduced cortical thickness with higher DERS scores were found in the MAP group (Table 4.6). The influence of potential confounders (level of education, nicotine, cannabis alcohol, and methaqualone use) was tested in additional analyses of covariance and no significant main effects on brain structures were obtained.

A number of exploratory correlational analyses were undertaken to investigate relationships between brain measures and clinical variables. In the MAP group, longer duration of abstinence from MA was significantly associated with lower PANSS total scores, $T = -.393$, $p = .025$, and lower PANSS general psychopathology scores, $r = -.566$, $p = .018$. However, no significant associations were found between brain measures and MA use variables such as onset, duration and abstinence, after FDR correction.

Table 4.5. Correlations between cortical thickness and Emotion Reactivity scores in MA-dependent individuals with and without a history of psychosis

	ERS-Total		ERS-Intensity		ERS-Persistence		ERS-Sensitivity	
brain region	*r*	*p*	*r*	*p*	*r*	*p*	*T*	*p*
MA group								
pars triangularis	.457	.037	.457	.037	.446	.043	.208	n.s.
MAP group								
lateral orbitofrontal	-.659	.002*	-.692	.001*	-.525	.021	-.348	.041
pars orbitalis	-.568	.011*	-.562	.012*	-.371	n.s.	-.445	.009
pars triangularis	-.555	.014*	-.557	.013*	-.399	n.s.	-.360	.034

Pearson's *r* and Kendall's *T* were calculated, with *p*-values of < 0.05 considered as statistically significant. n.s.-non-significant. *Marked results survive FDR correction for multiple comparison across eight regions of interest.

Table 4.6. Correlations between cortical thickness and Difficulties in Emotion Regulation scores in methamphetamine abusers with a history of psychosis

	DERS-Total		DERS-Awareness		DERS-Clarity		DERS-Goals		DERS-Impulse		DERS-Nonacceptance		DERS-Strategies	
brain region	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
inferior temporal	-.272	n.s.	-.494	.031	-.082	n.s.	-.619	.005*	-.330	n.s.	-.160	n.s.	-.435	n.s.
lateral orbitofrontal	-.491	.033	-.112	n.s.	-.501	.029	-.126	n.s.	-.368	n.s.	-.461	.047	-.459	.048
pars orbitalis	-.468	.043	.115	n.s.	-.468	.043	-.146	n.s.	-.529	.020	-.284	n.s.	-.572	.010
pars triangularis	-.410	n.s.	.093	n.s.	-.417	n.s.	-.162	n.s.	-.551	.014	-.276	n.s.	-.384	n.s.

Pearson correlation coefficient *r* was calculated. Correlations with *p*-values of < 0.05 were considered statistically significant. n.s.-non-significant. *Marked results survive FDR correction for multiple comparison across eight regions of interest. No statistically significant correlations were found for MA dependants without a history of psychosis.

4.4. Discussion

This MRI investigation of frontotemporal cortical and subcortical grey matter structures and their association with affect regulation revealed three main findings in MA and MAP. First, patients with MAP demonstrated cortical thinning in the left fusiform, inferior temporal, lateral and medial orbitofrontal, pars orbitalis and triangularis, and the insular cortex, when compared to MA-dependent individuals. Second, the MAP group showed a significant bilateral volume reduction in the hippocampus compared to the MA group (L -9.8%, R -9%). Third, in the MAP group, cortical thinning in lateral orbitofrontal cortex, inferior frontal and temporal gyrus was significantly associated with emotion dysregulation.

Our finding that cortical grey matter integrity in MAP is reduced is consistent with previous work using voxel-based morphometry (VBM) in MAP (which found deficits in inferior frontal gyrus) (Aoki et al., 2013). Our results are also supported by findings in subjects with first episode psychosis, e.g. a meta-analysis of volumetric studies found grey matter reductions in the inferior frontal area in such individuals (Fusar-Poli et al., 2011). Further, in schizophrenia, cortical thinning has been found in similar prefrontal and temporal regions as reported in the present study, including the inferior frontal, orbitofrontal, inferior temporal, and insular cortex (Kuperberg et al., 2003; Narr et al., 2005; Nesvåg et al., 2008). While regional cortical thinning may reflect underlying neuropathological abnormalities (Kuperberg et al., 2003; Nesvåg et al., 2008), the precise pathophysiological mechanisms involved remain poorly understood.

The present study also revealed bilateral reductions of hippocampus volumes in MAP compared to MA dependence. This is consistent with frequent reports of pathological hippocampus changes in MAP (Orikabe et al, 2011), in first episode and chronic schizophrenia (Velakoulis et al., 2006) and in individuals at high risk for psychosis (Fusar-Poli et al., 2011). While some studies have reported a decrease in hippocampal volumes in MA-dependent individuals it is unclear whether such studies excluded patients with MAP. Our finding of reduced hippocampal volume and reduced cortical thickness in regions of the prefrontal and temporal cortex further support the premise that MAP and schizophrenia are alike - not only in clinical symptoms, but also in underlying neuroanatomical abnormalities.

Contrary to our initial hypothesis, we identified an increase in cerebral thickness in MA-dependent individuals with no history of psychosis, compared to healthy controls. This structural change reached statistical significance in the entorhinal and insular cortex. To date, VBM studies in MA abuse have been inconsistent (Morales et al., 2012; Nakama et al., 2011; Schwartz et al., 2010); as have studies of surface-based morphometry in stimulant abuse, with some studies showing thinning (Koester et al., 2012), others thickening (Tanabe et al., 2013), and others no change (Lawyer et al., 2010). A number of factors may contribute to such inconsistency, including heterogeneous participant characteristics, type of stimulant used, scan parameters and analysis packages applied in the different studies. Further, gender-dependent effects of stimulants have also been reported, with females demonstrating thinner cortices, and males thicker cortices in the insula when compared to gender-matched controls (Tanabe et al., 2013). This is consistent with our finding of increased cortical thickness in the insula in our MA group, predominantly constituted by male participants.

Further work is needed to understand the underlying neurobiology of our finding of increased cortical thickness in MA. One possibility is that this represents a compensatory response to MA-induced ischemic or neurotoxic injury, thus pointing to inflammation or reactive microgliosis and astrocytosis (Sekine et al., 2008; Yamamoto et al., 2010). Prior preclinical studies have supported this explanation (Asanuma et al., 2004; LaVoie et al., 2004; Pu and Vorhees, 1990). Another potential response to MA neurotoxicity is an upregulation of brain-derived neurotrophic factor (BDNF) levels, as has been previously reported in humans (D.J. Kim et al., 2005) and rodents (Braun et al., 2011). Due to its involvement in neuronal growth, maintenance and survival, specifically of dopaminergic neurons (Hyman et al., 1991), BDNF may produce a neuroprotective mechanism against MA (Matsuzaki et al., 2004), and may thus contribute to the observed morphological abnormalities in MA-dependent individuals. It may be hypothesized that, in MAP, treatment with typical antipsychotics reduces inflammation or lowers BDNF (Pillai et al., 2006). Longitudinal studies are needed to determine whether MA dependence is associated with neuroplastic changes and increased grey matter thickness, and whether MAP in particular leads to a more pathological process that is accompanied by cortical thinning with increased cognitive and affective disturbances over time.

On the basis of MA-related structural abnormalities reported in brain regions involved in emotion regulation, we hypothesized that patients with MA dependence and MAP would demonstrate impaired emotion regulation abilities. In both study groups, we found that patients' ratings of emotion reactivity and difficulties in emotion regulation showed evidence of impairment, when compared to healthy controls. Although emotion dysregulation did not differ between MA and MAP, it is notable that emotion dysregulation was associated with cortical thinning in prefrontal and inferior temporal areas in the MAP group. This supports the argument that such thinning is associated with clinical symptoms. Prefrontal brain areas have been implicated in emotion processing, motivation and mood (Davidson & Irwin, 1999) as well as in emotion regulation in humans and animals (Quirk & Beer, 2006). Furthermore, temporal structures, including the ITG, have been reported to promote various socio-emotional processes, such as face evaluation (Haxby et al., 2000) and emotional scene processing (Sabatinelli et al., 2005). In schizophrenia studies, structural abnormalities in frontal and temporal brain areas have been related to impaired cognition and social functioning (Kuperberg & Heckers, 2000), and there is a growing body of evidence of hypoactivity in the PFC (Morris et al., 2012; Ursu et al., 2011) which disturbs the interaction between prefrontal control regions and subcortical areas associated with regulation of emotion. Taken together, these findings suggest a close link between prefrontal brain alterations and emotion dysregulation across disorders, but particularly in MAP. Drug abuse rehabilitation should arguably include a strong focus on emotion regulation skills.

Several limitations of the current study should be noted. First, all MA-dependent individuals with a history of psychosis had received antipsychotic medication, either currently or in the past. The effects of first-generation neuroleptics on brain structure are heterogeneous and may not be seen in all patients. A number of reviews on the effects of antipsychotic drugs in patients with schizophrenia have highlighted findings of volume increase in the basal ganglia, volume decrease in parietal and frontal cortices, or no changes in brain volumes (Navari & Dazzan, 2009; Scherk & Falkai, 2006; Smieskova et al., 2009). While it is ideal for non-medicated patients to be studied, this is often logistically impossible (e.g. in more severe cases of psychosis). However, we did exclude participants who had been on treatment for longer than three months at the time of recruitment.

Second, due to the high prevalence of polysubstance abuse in our setting, it was not feasible to recruit individuals who used only MA. Thus, most of our study participants also used marijuana, methaqualone and/or nicotine. However, no differences were apparent between the two MA-abusing groups and no statistically significant main effects of additional substance use on brain structure were detected.

Third, individuals with comorbid psychiatric disorders were excluded from this study, given known alterations in brain imaging associated with such conditions. This may have resulted in a non-representative study cohort, as depression and anxiety disorders are common among individuals with MA dependence and MAP.

In conclusion, a direct comparison of MA-dependent patients with and without a history of psychosis revealed significant differences in cortical thickness between MA and MAP. While the present study found increased cortical thickness in MA participants, a decrease in frontotemporal cortical thickness and hippocampal volume was shown in MAP, which is consistent with imaging findings in other psychotic disorders. Our behavioural data support the hypothesis that MA use is associated with deficient affect regulation abilities, and MRI results suggest that this impairment is related to cortical thinning in MAP.

Chapter 5

Study 3: Impulsivity and reduced white matter integrity in methamphetamine dependence with and without a history of psychosis

The previous chapter showed that both individuals with MA dependence and MAP report higher levels of emotion reactivity and difficulties in emotion regulation than healthy controls, but demonstrate distinct patterns of cortical grey matter deficits. Poor affect regulation is thought to be closely linked to impulsivity (Gratz & Roemer, 2004; Whiteside & Lynam, 2001) and it is therefore to be expected that structural grey and white matter abnormalities in the circuitry of affect regulation may play a role in the development of impulsive behaviour (Davidson et al., 2000; Lim et al., 2008). MA dependence has previously been characterised by high levels of impulsiveness, resulting in hostility, aggressive behaviour and mental health issues (Dawe et al., 2009; Lapworth et al., 2009). This chapter assesses white matter integrity and its association with impulsivity in individuals with MA dependence and MAP.

5.1. Introduction

Emerging evidence from human and animal research suggests that abuse of the psychostimulant MA has severe neurotoxic effects, including white matter damage in the form of axonal degeneration and microglial activation (Barr et al., 2006; Krasnova & Cadet, 2009). But only recently have brain imaging techniques, especially diffusion tensor imaging (DTI), advanced as non-invasive tools to assess brain white matter pathology. Research studies using magnetic resonance imaging or spectroscopy have reported a variety of white matter abnormalities in MA dependence, specifically hypertrophy in the temporal and occipital lobes (Thompson et al., 2004) as well as decreased levels of neuronal integrity markers and increased levels of glial markers in frontal brain areas (Ernst et al., 2000; Sung et al., 2007). Additionally, converging evidence points to the involvement of white matter abnormalities in psychiatric disorders such as MAP (Aoki et al., 2013; Howells et al., 2014), bipolar disorder (Barysheva et al., 2013) and schizophrenia (White et al., 2013).

Moreover, impaired cognitive control processes have been associated with MA abuse, leading to behavioural changes characterized by high levels of impulsiveness, hostility and aggression (Dawe et al., 2009; Plüddemann et al., 2010). In addition to growing evidence that grey matter abnormalities in fronto-striatal networks potentially underlie impulsivity and affect regulation in addiction (Goldstein & Volkow, 2011; Moreno-Lopez et al., 2012; Quirk & Beer, 2006; Schwartz et al., 2010), there are data indicating that white matter pathology contributes to the inability to inhibit impulsive acts (Lim et al., 2008; Moeller et al., 2005). In MA abuse, decreased glucose metabolism was found in frontal white matter, which was associated with impairment in frontal executive function (S.J. Kim et al., 2005). Thus, the investigation of white matter integrity is important for a better understanding of the neural basis of impulsivity in MA dependence.

Recently, DTI has enabled the examination of white matter microstructural integrity (Le Bihan et al., 2001) that might not be revealed by conventional brain imaging. DTI is a sensitive imaging technique that quantifies the magnitude and directionality of tissue water mobility, which is highly sensitive to differences in membrane microstructural architecture. Information about brain microstructural white matter organization can be derived from fractional anisotropy (FA) and mean diffusivity (MD). FA reflects the orientation specificity of water diffusion in white matter. A decrease in FA can refer to white matter damage in relation to fibre tract coherence, fibre diameter, packing density and degree of myelination (Alexander et al., 2007). MD, in turn, represents the degree of water diffusion regardless of fibre directionality and is calculated as the average of the three tensor eigenvalues. An increase in MD can refer to loss of white matter integrity relating to changes in intercellular space and compactness (Beaulieu, 2002). Nonetheless, due to the complex fibre architecture and an orientation uncertainty, direction of the measured tensor eigenvalues does not always correspond with the underlying structure, especially in pathological tissue (Wheeler-Kingshott & Cercignani, 2009). In addition, interpretation of changes to the diffusion tensor is complicated by its sensitivity to image noise, artefacts and crossing fibres, and hence should be done with care (Alexander et al., 2007).

To date, only a few studies have used DTI in MA dependence, and all of them have employed a voxel or region of interest (VOI, ROI) approach. Primarily, these studies investigated the corpus callosum and reported reduced FA in the genu (Kim et al., 2009; Salo et al., 2009; Tobias et al., 2010), a structure involved in the interhemispheric transfer of information and projection into various frontal brain areas. In addition, white matter abnormalities were detected in frontal brain areas (Chung et al., 2007; Tobias et al., 2010), and the dorsal striatum (Alicata et al., 2009), but not in parietal or occipital areas (Chung et al., 2007). No study has previously assessed white matter integrity in MAP using DTI. However, data from schizophrenia research indicate widespread white matter abnormalities in the brain, including the brain stem and cerebellum (Kyriakopoulos et al., 2008).

Consistent with the notion of there being cognitive and emotional dysregulation in MA dependence, reported white matter changes have been shown to be associated with problems in cognitive control (Chung et al, 2007; Kim et al., 2009; Salo et al., 2009), addiction severity (Alicata et al., 2009) as well as psychiatric symptoms (Tobias et al., 2009). But the relationship between impulsive behaviour and measures of white matter abnormalities in MA and especially MAP remains less clear.

The present study compared white matter integrity in MA dependence with and without a history of psychosis and healthy controls, using fully automated tract-based spatial statistics (TBSS) (Smith et al., 2006). As we expected multi-regional white matter pathology in the MAP group (based on findings in psychosis research), we chose this whole brain analytic approach, allowing for investigation in entire neural networks and not only in predefined regions of interest. We hypothesized that in both MA-dependent groups white matter structure would be affected, while greater effects and an association with psychotic symptoms were expected in the MAP group. We further investigated how the three study groups differ in five distinct facets of impulsivity and expected higher levels of impulsivity in MA and MAP that would relate to altered microstructural integrity.

5.2. Methods

5.2.1. Participants

One hundred and nine participants, comprising 30 MAP patients, 39 participants with MA dependence and no psychosis (MA group), and 40 healthy controls (CTRL group), took part in this study. All participants were right-handed and matched for age and gender. Route of MA use was by smoking of the crystals exclusively. The patients were recruited from drug rehabilitation facilities and hospitals in Cape Town. Control participants were recruited from local communities using advertisements, and by word of mouth. Clinical assessment was carried out by trained staff of the Department of Psychiatry and Mental Health, University of Cape Town (UCT), using the SCID-I for DSM-IV-TR (First et al., 2002). Positive and negative symptoms within the MAP group were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Participants were excluded from the study if they presented with: 1) additional substance dependencies other than nicotine for the MA and MAP groups, and any substance dependence in the control group; 2) a lifetime and current diagnosis of any psychiatric disorders (other than MA dependence and MAP in the MA and MAP groups); 3) a history of psychosis prior to MA abuse; 4) a medical or neurological illness or head trauma; 5) a seropositive test for HIV; 6) MRI incompatibilities or known claustrophobia. All participants in the MAP group were on treatment with neuroleptic medication, but treatment longer than twelve weeks at the time of scanning was an additional exclusion criterion for the MAP group.

5.2.2. Impulsivity Measure

The UPPS-P impulse behaviour scale (Cyders et al., 2007) assesses five distinct dimensions of impulsivity: Negative Urgency, lack of Premeditation, lack of Perseverance, Sensation Seeking, and Positive Urgency. This 59-item inventory employs a 4-point Likert-type response format (1 = Agree Strongly, 2 = Agree some, 3 = Disagree some, 4 = Disagree strongly). The negative and positive urgency dimensions refer to the tendency to engage in impulsive behaviours under the condition of high negative and high positive affect, respectively. Lack of premeditation refers to non-planning impulsiveness and assesses one's ability to think through potential consequences of one's actions. Lack of perseverance reflects poorer concentration and increased distraction, usually on boring or difficult tasks. Lastly, sensation seeking measures the tendency to seek excitement and stimulation. Due to time restrictions or follow-up issues, some data were missing in this study; specifically two MA, three MAP and three CTRL participants did not complete the UPPS-P.

5.2.3. Statistical Analysis

Statistical analysis of demographic, clinical and questionnaire data was performed using the SPSS 22.0 statistical package (Armonk, NY: IBM Corp). The assumption of normality of each continuous variable was analyzed with the Shapiro-Wilk test, and all datasets appeared to be non-normally distributed. Consequently, all group comparisons were done using Kruskal-Wallis tests and follow-up Mann-Whitney tests. Nominal data were compared using chi-square tests.

To examine the relationship of impulsivity scores with MA use measures (age of onset, duration of use, duration of abstinence) and ROI measures of FA and MD, Spearman's correlation coefficient was calculated.

The Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to correct for multiple testing. For all analyses p-values of $< .05$ (two-tailed) were considered statistically significant.

5.2.4. Diffusion Tensor Imaging

Diffusion tensor images were acquired on a Siemens Magnetom 3-T Allegra scanner at the Cape Universities Brain Imaging Centre, equipped with a CP single channel head coil. The scanning parameters were as follows: TR = 9500 ms, TE = 88 ms, field of view = 240 mm, slice thickness = 2 mm, slices = 70. Diffusion was measured along 30 directions. For each slice and gradient direction, two images were acquired: with diffusion weighting (b = 1000 s/mm^2) and a single unweighted volume (b = 0 s/mm^2). This sequence with a scan time of 5.33 min was repeated three times.

5.2.5. DTI Data Processing and Analysis

DTI processing was performed using the FSL 5.0.2 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). After correction for eddy-current distortions, the three acquisitions were exported to Matlab R2013b. Outlier data points were rejected by calculating the Z-values of the data distribution and discarding any points more than three standard deviations from the mean. Afterwards the corrected acquisitions were affine registered to create a mean DTI image. The mean image was corrected for head motion and brain extraction was applied. At each voxel a diffusion tensor model was fitted to the data and any outliers were removed. Finally, images of FA as well as MD were derived from the model.

Whole brain voxelwise statistical analysis of the diffusion-tensor derived measures (FA, MD) was carried out using tract-based spatial statistics (TBSS) (Smith et al., 2006). First, nonlinear registration was used for spatial normalization of DTI data to the Montreal Neurological Institute (MNI152) space. Next, a mean FA image was created (threshold of 0.2) and thinned to create a mean FA skeleton representing the centres of all tracts, i.e. the most compact whole brain white matter, common to all participants. Each participant's aligned DTI measures were then projected onto this skeleton.

For analysis of group differences among the DTI measures a voxelwise permutation-based non-parametric inference was performed using FSL’s randomize tool (Winkler et al., 2014). First, a general linear model (GLM) was set up for analysis of covariance, with age and gender as nuisance covariates. The primary analysis of main effect of group and follow-up direct comparisons of the three study groups (in six pairwise contrasts: CTRL>MA, CTRL>MAP, MA>CTRL, MA>MAP, MAP>CTRL, MAP>MA) were tested with 10,000 random permutations. Results were corrected for multiple comparisons by the threshold-free cluster enhancement (TFCE) method with family-wise error (FWE) correction. The threshold for significance was set at $p < .05$. We consulted the "JHU ICBM-DTI-81 White Matter Labels Atlas" (Mori et al., 2008) and the "JHU White Matter Tractography Atlas" (Hua et al., 2008) in FSL to identify the most probable anatomical localization of each cluster showing significant between-group differences. To achieve a more straightforward visualization of the skeletonised results, we employed the "tbss_fill" script to thicken the results somewhat.

New GLMs were set up to investigate associations of white matter abnormalities with psychotic symptoms (PANSS scores) and MA use measures in the MAP group. The relationship between white matter abnormalities and MA use measures was also assessed in the MA group, applying a contrast mask to include only those voxels with significant group differences (this masking was not applied in the MAP group given the global nature of group differences). Again, age and gender were entered into the models as covariates of no interest. The voxelwise statistical analysis with FSL's randomize tool remained as described above.

Based on the reviewed literature, the relationship with impulsivity was assessed in a priori defined structures of interest found, at least partially, in frontal areas of the brain. These included the genu and body of the corpus callosum, the anterior corona radiata, cingulum, uncinate fasciculus and the superior longitudinal fasciculus, based on the ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008). With a customized script, mean FA and MD values were extracted from those regions for further correlational analyses with UPPS-P subscales.

5.3. Results

5.3.1. Demographics and Substance Use

There were no significant differences in age and gender distribution between the three study groups (Table 5.1). However, the control group had significantly higher levels of education compared to the MA, $U = 477.5$, $p = .002$ and MAP groups, $U = 235.5$, $p < .001$. Across both MA-dependent groups, participants did not differ in MA use variables (i.e. duration and onset of use, and duration of abstinence). However, controls smoked significantly less cigarettes than either the MA group, $\chi^2(1) = 8.19$, $p = .004$, or the MAP group, $\chi^2(1) = 12.34$, $p < .001$. Further, there was a significantly lower methaqualone use in CTRL relative to MA, $\chi^2(1) = 5.48$, $p = .02$, in CTRL relative to MAP, $\chi^2(1) = 17.4$, $p < .001$, and in MA relative to MAP, $\chi^2(1) = 5.41$, $p = .021$.

Table 5.1. Demographic and clinical information for MA-dependent individuals with and without a history of psychosis and healthy controls

Demographic Measures	MA n=39	MAP n=30	CTRL n=40	test for group difference
male/female, n	28/11	23/7	29/11	$\chi^2(2)=.232, p=.926$
Age in years, median (range)	26 (18-38)	22.5 (19-41)	25 (18-38)	$H(2)=2.41, p=.299$
Level Of Education in years, median (range)	10 (8-15)	10 (6-15)	12 (9-14)	$H(2)=19.9, p<.001$
Tobacco smokers in last year, n	33	28	22	$\chi^2(2)=16.27, p<.001$
Alcohol consumers in last year, n	20	9	17	$\chi^2(2)=3.15, p=.207$
Cannabis users in last year, n	10	14	14	$\chi^2(2)=3.30, p=.192$
Methaqualone users in last year, n	5	11	0	$\chi^2(2)=18.57, p<.001$
MA Use Measures				
Age at first use in years, median (range)	17 (12-32)	17 (12-40)		$U=504.5, p=.327$
Duration in years, median (range)	6 (1.5-19)	6.5 (1-18)		$U=534.0, p=.535$
Abstinence in days, median (range)	21 (1-240)	41 (1-270)		$U=455.5, p=.116$
Clinical Measures				
Neuroleptic Medication in days, M±SD (range)		44.5±19 (14-85)		
PANSS negative symptoms, median (range)		9 (7-37)		
PANSS positive symptoms, median (range)		10.5 (7-29)		
PANSS psychopathology, median (range)		22 (16-46)		

PANSS: Positive and Negative Syndrome Scale. M: mean, SD: standard deviation.

5.3.2. Behavioural Measures

Table 5.2 summarizes descriptive UPPS-P scores, group statistic and pairwise comparisons for the MA, MAP and CTRL groups. Both MA-abusing groups showed higher impulsivity scores than the CTRL group, but no differences were found between the MA and MAP groups. Impulsivity scores showed no significant correlation with MA use variables (in both MA-dependent groups) or clinical measures (in MAP group) that survived correction for multiple testing.

Table 5.2. Mean scores and group comparisons of distinct impulsivity dimensions for MA-dependent individuals with and without a history of psychosis and healthy controls

					Group comparisons					
				Group Statistic	MA – CTRL		MAP - CTRL		MA - MAP	
UPPS-P dimensions	MA	MAP	CTRL	*H*(2)	*U*	*p*	*U*	*p*	*U*	*p*
Negative Urgency	34 (18 – 44)	33 (18 – 45)	25 (15 – 48)	21.27**	315.5	<.001	215.0	<.001	492.5	.924
lack of Premeditation	21 (11 – 33)	21 (12 – 35)	19 (11 – 33)	$4.85^{n.s.}$						
Lack of Perseverance	18 (11 – 30)	21 (13 – 29)	16 (10 – 27)	8.96*	515.5	.067	279.0	.003	420.0	.278
Sensation Seeking	35 (12 – 48)	35 (27 – 48)	34 (15 – 47)	$0.707^{n.s.}$						
Positive Urgency	35 (14 – 53)	38 (22 – 55)	24 (15 – 53)	24.74**	350.0	<.001	157.5	<.001	393.5	.149

UPPS-P scores are displayed in median (range). *H*: Kruskal –Wallis test, *U*: Mann-Whitney test. * $p < .05$, ** $p < .001$, n.s. - non-significant. Significant results within each subscale survive FDR correction.

5.3.3. TBSS Main Effects of Group

Covarying for age and gender, we detected four clusters showing a significant main effect of group for FA, comprising the bilateral cerebral peduncle (MNI x,y,z: -15,-22,-12; F_{max} = 10.2; voxels = 241, and MNI x,y,z: 13,-11,-11; F_{max} = 18; voxels=142), left corticospinal tract (MNI x,y,z: -18,-27,53; F_{max} = 13.3; voxels = 33) and the left anterior thalamic radiation (MNI x,y,z: -7,-3,0; F_{max} = 9.28; voxels = 20). For MD, a main effect of group was found in widespread areas covering almost the entire white matter skeleton (MNI x,y,z: 21,-26,40; F_{max} = 19.9; voxels = 58583).

5.3.4. TBSS Group comparisons

MA versus CTRL

The MA group relative to CTRL exhibited several clusters of increased MD in the right hemisphere (3734 voxels), comprising the internal capsule, cingulum, forceps minor, corticospinal tract, corona radiata, and the anterior thalamic radiation (Figure 5.1A). Only one cluster (34 voxels) of significantly increased MD was found in the left hemisphere, specifically in the posterior limb of the internal capsule.

No FA differences were revealed between the MA and CTRL groups.

MAP versus CTRL

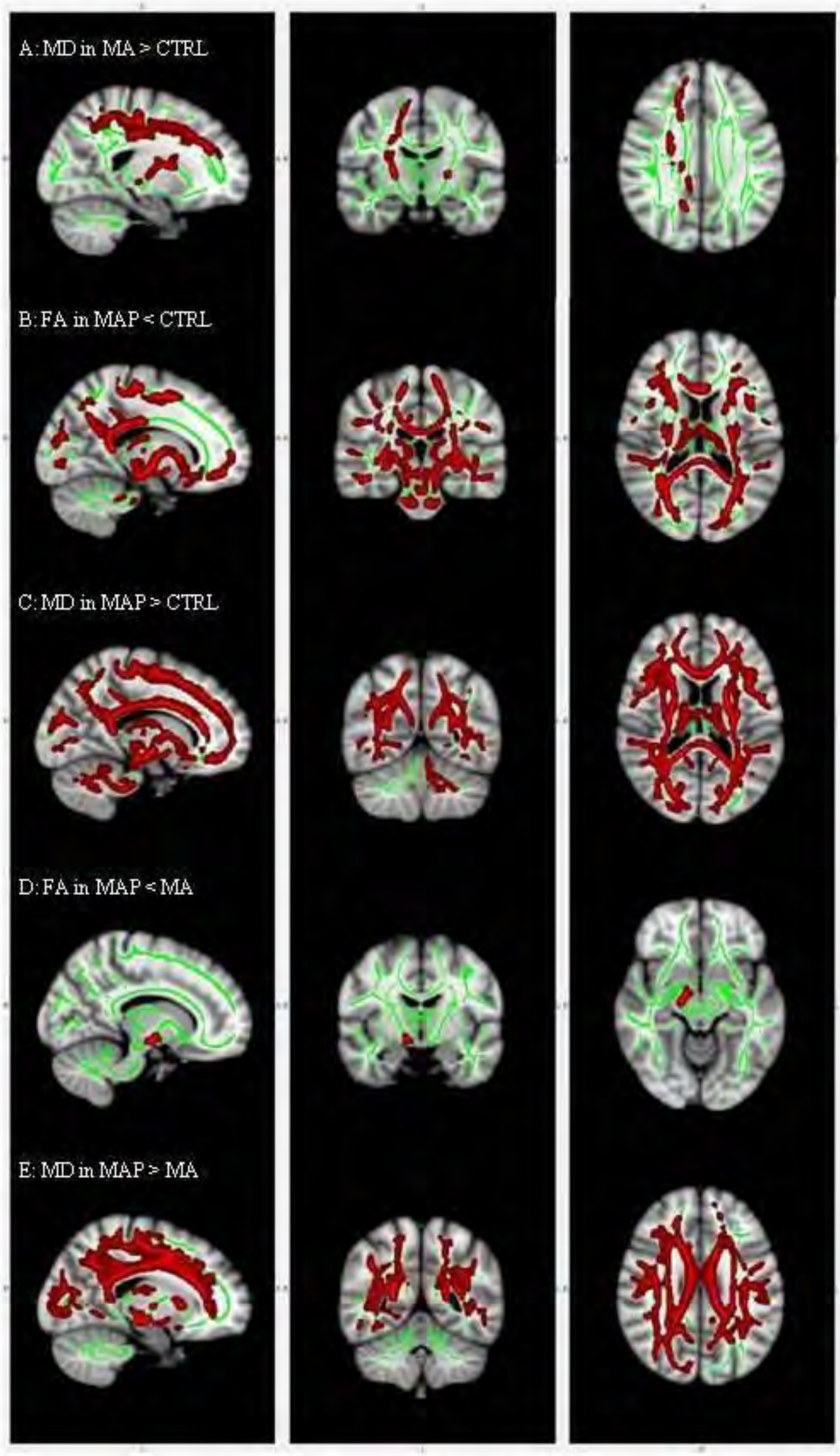
Compared to healthy controls, MAP patients showed significantly reduced FA in a widespread cluster (48020 voxels) extending into frontal, temporal, parietal and occipital white matter bilaterally. Reduced FA was found in all major white matter tracts, e.g. the corticospinal tracts, longitudinal fasciculi, fronto-occipital fasciculi, uncinate fasciculi, thalamic radiations, corpus callosum, cingulum, internal and external capsule, and cerebral peduncle (Figure 5.1B).

MD in MAP patients was significantly increased in a widespread cluster (78745 voxels) covering all major white matter areas even more extensively than FA changes in the reported areas, except for the right cerebellum (Figure 5.1C).

MAP versus MA

MAP patients relative to MA exhibited significantly lower FA values in only one cluster (90 voxels) comprising parts of the right cerebral peduncle, corticospinal tract and anterior thalamic radiation (Figure 5.1D).

The MAP group also exhibited significant increases in MD in extensive cerebral white matter areas (49993 voxels), when compared to the MA group (Figure 5.1E). No differences were found in the cerebellum between the two groups.


A: MD in MA > CTRL

B: FA in MAP < CTRL

C: MD in MAP > CTRL

D: FA in MAP < MA

E: MD in MAP > MA

Figure 5.1. Group differences in mean diffusivity (MD) and fractional anisotropy (FA) covaried for age and gender ($p<.05$, corrected for multiple comparisons). Significant clusters (red) are thickened to enhance visualization. Slices in MNI coordinates x,y,z: A = 70,113,104; B = 105,101,87; C = 104,70,88; D = 77,118,62; E = 72,76,100.

5.3.5. TBSS Correlations

MA abstinence correlation in MA group

In the MA group, correlational analyses revealed a positive relationship between MD values and MA abstinence in three clusters of the right hemisphere, comprising frontal white matter (MNI x,y,z: 10,-16,66; t_{max} = 6.32; r = .72; voxels = 121) and the superior corona radiata (MNI x,y,z: 24,-8,34; t_{max} = 4.25; r = .57; voxels = 100), (MNI x,y,z: 18,1,41; t_{max} = 3.6; r = .51; voxels = 71) (Figure 5.2A).

MA abstinence correlation in MAP group

In the MAP group, lower MD correlated with longer MA abstinence, represented in an extensive cluster (Figure 5.2B) including frontal, temporal and subcortical white matter (MNI x,y,z: -22,-21,-3; t_{max} = 5.56; r = -.74; voxels = 16844). MA abstinence was also associated with higher FA (Figure 5.2C) in even more widespread white matter areas (MNI x,y,z: -35,-52,-12; t_{max} = 7.4; r = .83; voxels = 60161).

PANSS correlation in MAP group

In the MAP group, we detected four clusters indicating a significant relationship between higher scores on the PANSS negative symptoms subscale and increased MD values (Figure 5.2D), which covered areas of the splenium (MNI x,y,z: 16,-34,29; t_{max} = 4.42; r = .169; voxels = 218) and body (MNI x,y,z: -13,-23,30; t_{max} = 4.72; r = .196; voxels = 72) of the corpus callosum, the right posterior corona radiata (MNI x,y,z: 22,-28,31; t_{max} = 3.65; r = .104; voxels = 35), and parietal white matter (MNI x,y,z: 15,-48,61; t_{max} = 4; r = .132; voxels = 129). No relationship was detected between FA or MD values and scores of the PANSS positive symptom and general psychopathology scales, or duration of neuroleptic treatment.

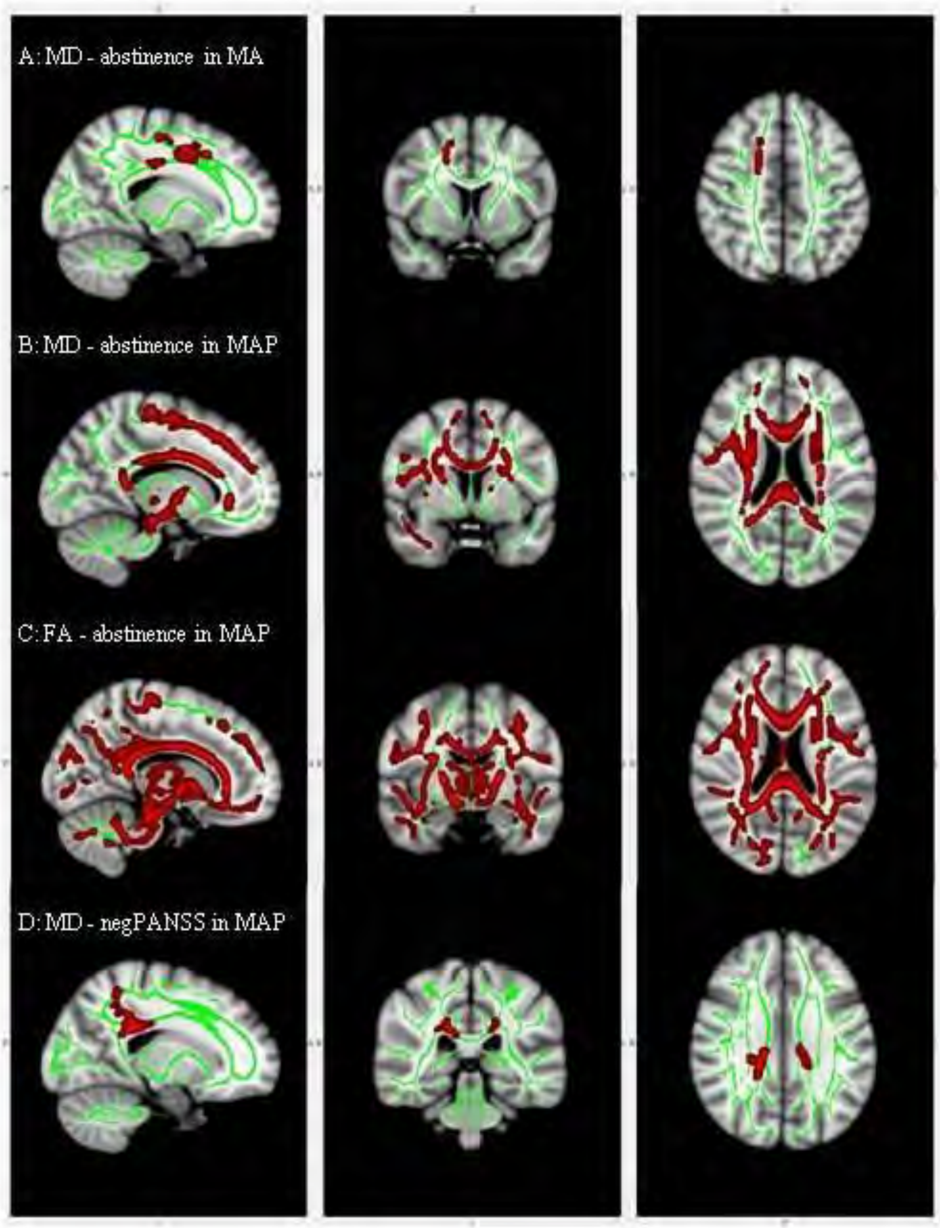


Figure 5.2. Correlations of mean diffusivity (MD) and fractional anisotropy (FA) with duration of abstinence from MA and negative psychotic symptoms covaried for age and gender ($p<.05$, corrected for multiple comparisons). Significant clusters (red) are thickened to enhance visualization. Groups: MA-methamphetamine dependent individuals, MAP-methamphetamine-associated psychosis patients. Slices in MNI coordinates x,y,z: A = 72,134,118; B = 103,130,93; C = 78,117,93; D = 72,93,102.

5.3.6. ROI Impulsivity Correlation

To examine the relationship of the three impulsivity subscales, that showed significant between-group differences, with FA and MD values in the pre-selected regions of interest, Spearman correlation analysis was done. After FDR correction, a significant positive correlation between MD in the right anterior corona radiata and negative urgency scores (r_s = .652, p < .001) as well as positive urgency scores (r_s = .655, p < .001) was revealed in the MAP group.

5.4. Discussion

This DTI investigation of whole brain white matter integrity and its association with impulsivity revealed three main findings in MA and MAP. First, compared to healthy controls, MA-dependent individuals showed distinct clusters of diminished white matter integrity as indicated by increased MD in the projection fibres of the internal capsule and in association fibres connecting the frontal lobe with posterior regions of the brain. Second, patients with MAP demonstrated a global reduction in white matter integrity as evidenced by reduced FA and increased MD values, relative to both healthy controls and MA-dependent individuals; and greater MD values correlated significantly with negative psychotic symptoms. Third, both MA-abusing study groups showed increased self-report levels of impulsivity, which was significantly associated with increased MD in the right corona radiata in the MAP group.

Our findings of increased MD in white matter tracts comprising the internal capsule (which separates the caudate nucleus from the putamen and globus pallidus) and its projection fibres in the MA group are to some extent in keeping with reported subcortical white matter abnormalities in MA. A study by Alicata et al. (2009) showed that MA users had higher diffusion in the left caudate nucleus and bilaterally in the putamen, while FA remained unchanged in these striatal structures. In addition, frontal white matter tract abnormalities have previously been found, and were associated with deficits in cognitive control as well as psychiatric symptoms in MA (Chung et al., 2007; S.J. Kim et al., 2005; Tobias et al., 2010). In addition, findings of higher MD in several white matter tracts, including the corticospinal tract, cingulum and anterior thalamic radiation suggest that MA affects additional fibre tracts, passing between functional networks integrating sensorimotor, cognitive, and emotional information. Connecting the cortex with parts of the striatum, damage to the internal capsule and its projection fibres may further support the notion of corticostriatal dysfunctions in individuals who abuse MA (London et al., 2014).

The fact that we detected increased MD, but no changes in FA, might indicate that those brain regions rather underwent increases in the spacing between membrane layers or increases in water content due to tissue inflammation or myelin loss, than having experienced axonal loss (Alexander et al., 2007; Beaulieu, 2002). Inflammatory processes and associated microgliosis in striatal and frontal brain areas due to MA abuse have been proposed by several studies of different imaging modalities (Schwartz et al., 2010; Sekine et al., 2008; Thompson et al., 2004). Furthermore, preclinical studies have supported this notion of neuroinflammation after MA exposure (Asanuma et al., 2004). An alternative explanation for increased MD values might be that MA abusers develop a pathology resembling chronic ischemic lesions, since long-term reductions in global and regional cerebral blood flow in subcortical and prefrontal brain areas have been shown in abstinent MA abusers (Chung et al., 2010).

In MA-associated psychosis, white matter changes were found to be widespread. In keeping with our hypothesis, the MAP group showed a global increase in MD together with an extensive reduction of FA values. An increase in MD is, as discussed before, likely related to inflammatory processes and increased water content in the brain. The additional observation of decreased FA, however, may indicate injury to the axonal fibre. While no study has examined white matter microstructure in MAP before, many DTI studies in schizophrenia have found decreased FA and increased MD in fibre bundles across the frontal, temporal, parietal, and occipital lobes (Kubicki et al., 2007; Kyriakopoulos et al., 2008). This suggests a general disorganization of axon fibre architecture rather than a focal damage. Similarly, FA and MD changes reported in the present study highlight a possible interruption of diffusion along axon fibres in widespread areas of the brain in patients with MAP. In any case, efficient communication between brain circuits depends on myelination of axons to facilitate fast saltatory signal transmission. There is growing evidence pointing to widespread changes in the cells responsible for myelination, oligodendrocytes; and degenerative changes in myelinated fibres have previously been implicated in the pathophysiology of schizophrenia (Takahashi et al., 2011). There is also evidence for MA-induced cytotoxicity in oligodendrocytes leading to cell death (Genc et al., 2003), which may exacerbate the effects of additional susceptibility factors for white matter damage and the development of psychosis in some MA-dependent individuals. Supportive of this notion is the observation in the present study that MD and FA values improve with ongoing abstinence from the drug.

In direct comparison to the MA group, MAP showed widely distributed significant MD increase in addition to FA reduction in the midbrain, comprising the right cerebral peduncle, anterior thalamic radiation, and corticospinal tract. The midbrain is the centre of visual and auditory reflexes, integrating sensory information and transmitting decisions to motor neurons. Reduced white matter connectivity in this area might well underlie the auditory and visual hallucinations frequently experienced by MAP patients. Further, the anterior thalamic radiation carries nerve fibres between the thalamus and prefrontal cortex and abnormalities therein have been linked with impaired executive functioning, but not psychotic symptoms in schizophrenia (Mamah et al., 2010).

In the present study, negative psychotic symptoms correlated with MD in the corpus callosum, posterior corona radiata and parietal white matter (precuneus area). This result, in addition to the finding of degraded white matter in extensive brain areas, may provide new evidence for the involvement of disrupted white matter integrity in the pathology of MA-associated psychosis. In schizophrenia, degraded white matter near the right insula has been shown to correlate with the PANSS negative symptoms subscore (Shin et al., 2006). The precuneus and insula share a role in self-attribution processes (Cabanis et al., 2013) and structural impairment in these regions may result in mental disengagement. Additionally, structural disruption in the precuneus and other parts of the parietal lobe has previously been related to poor awareness of illness and problems in patients with psychosis (Cooke et al., 2008).

The observed reduced white matter integrity in the posterior parts of the corpus callosum, which transmits information between the two cerebral hemispheres, may further contribute to the impaired integration of information in MAP.

Scores on the negative and positive urgency subscales of the UPPS-P were significantly higher for the two MA-dependent groups, compared to CTRLs. Therefore, in MA abuse with and without a history of psychosis heightened negative or positive affect may lead to inhibition difficulties. This finding is in keeping with recent studies showing that urgency was most strongly associated with substance use problems and dependence (Verdejo-Garcia et al., 2007; Stautz & Cooper, 2013). The amplified tendency to give in to strong impulses may stem from poor emotion regulation and result in limited ways of responding, as seen in the high relapse rates in MA. In this light, interventions focusing on emotion regulation strategies to decrease urgency may achieve greater favourable preventive effects. Our finding of heightened impulsivity levels is in line with previous reports in MA abuse (S.J. Kim et al., 2005; Semple et al., 2005). However, the present study did not find an association of impulsivity scores with MA use onset, duration or abstinence, or with psychotic symptoms. This could possibly be ascribed to the self-report nature of all these measures, introducing the potentially confounding factor of unreliability.

We further tested if disconnected frontal white matter might be associated with high levels of impulsivity and found a significant correlation for MD in the right corona radiata with negative and positive urgency in MAP. This is in partial support of our initial hypothesis and also in keeping with previous findings of reduced white matter integrity in frontal brain areas, amongst others, relating to impulsivity measures in schizophrenia (Hoptman et al., 2004). Of note, we found significant FA or MD correlations with impulsivity scores in all tested frontal white matter tracts in the three study groups, but results did not survive correction for multiple testing.

Several cautionary notes should be pointed out regarding this study. First, all MAP patients were on neuroleptic treatment, which may have impacted the results. While some studies reported a correlation of antipsychotic medication and reduced FA in frontal lobe areas (Minami et al., 2003; Wang et al., 2013), most DTI studies in schizophrenia did not observe an effect on white matter microstructure (Kyriakopoulos et al., 2008). Similarly, in our study we found no evidence for a relationship between medication duration and DTI measures. Secondly, exact fibre tract identification in clusters that emerged from the different analyses is still difficult in areas where different tracts run together or cross. Also a definite interpretation of changes in the tensor-derived measures in terms of underlying microstructural white matter injury, including demyelination, degradation of membranes, and axonal loss, is not yet possible. Thirdly, the present study only included a self-report measure of impulsivity and reliability of given answers may be questionable at times. The inclusion of behavioural measures of impulsivity might have helped to validate the results. Finally, the cross-sectional nature of our data does not permit us to make any causal statement regarding the relationship between MA use and impulsivity. It might well be that individuals who have a predisposition to elevated levels of impulsivity are more likely to engage in drug use. Alternatively, long-term use of MA may result in elevated levels of impulsivity due to its neurotoxic effects on the brain. Longitudinal data and prospective research designs are needed to address this issue of causality as well as the issue of developing white matter changes as addiction and related psychopathology progress.

In summary, the use of an automated voxelwise whole brain method for analysis of DTI data has provided new information on how white matter is affected in MA dependence. The present study demonstrated different patterns of impaired white matter connectivity in MA and MAP, with corticostriatal networks being affected in MA, while MAP shows globally reduced white matter integrity similar to that seen in schizophrenia. In MAP, indices of disordered neuronal architecture in posterior brain parts were associated with psychotic symptoms, while frontal white matter pathology related to impulsive behaviour.

Chapter 6

Study 4: Corticolimbic functionality during affect labelling in methamphetamine dependence with and without a history of psychosis

After having highlighted the differences in structural brain deficits in individuals with MA dependence and MAP in the two previous chapters and showing that in MAP, structural grey and white matter alterations were associated with increased levels of emotion reactivity, emotion dysregulation and impulsivity, this chapter discusses MA-related functional brain deficits. Humans engage in affect regulation routinely; this usually happens intentionally to modify emotional behaviour. However, underlying regulatory processes can also be elicited incidentally when cognitively engaging with an emotional stimulus, but without explicit intentions to modify emotional responses (Hariri et al., 2000; Lieberman et al., 2007). This final study used fMRI to examine neural processes involved in intrinsic emotion processing and emotion regulation in both MA-dependent groups, compared to healthy controls.

Some caution must be taken when interpreting the output of an fMRI experiment, in particular when reading about increases and decreases in activity in certain brain areas. In fMRI, models are used to determine the blood oxygenation level-dependent (BOLD) signal derived from the amount of deoxygenated haemoglobin surrounding a confined neuronal population. This imaging technique relies on the fact that neuronal activation and its associated increase in energy use are linked with cerebral blood flow. However, the ratio between oxygenated and deoxygenated haemoglobin is only an indirect measure of neuronal activation, as other physiological processes, including glial cell blood supply and differences in the speed of oxygen consumption or in blood flow, may interfere with the signal measured. Further, the observed effects are relative and not individually quantitative, as they are related to the contrasts defined by the researcher. Nevertheless, fMRI is a popular and relevant non-invasive technique in neuroscience for measuring changes in brain activation in clinical populations.

6.1. Introduction

The loss of ability to cope adaptively with emotional events may contribute to adverse life consequences (Baicy & London, 2007). Frequently, MA abuse has been associated with aggressive tendencies and antisocial behaviour (Payer et al., 2011; Plüddemann et al., 2010; Watt et al., 2014), most likely due to a reduced ability to regulate negative, hostile feelings and behaviours (Homer et al., 2008). Impaired emotion processing and regulation are central features in many psychiatric disorders (Phillips et al., 2003b; Taylor & Liberzon, 2007). In substance use disorders, impaired regulation abilities may impact negatively on continuous drug use behaviours (Cheetham et al., 2010), aggression (Davidson et al., 2000), social function (Homer et al., 2008), and treatment outcome (Baicy & London, 2007).

The amygdala seems to be a key structure in the automatic detection and processing of affective stimuli and the generation of behavioural responses (Adolphs, 2002; Anderson & Phelps, 2002). Faces expressing negative emotions elicit especially high responsivity in this structure (Hariri et al., 2002). The recognition of emotional stimuli, however, is facilitated by loops between the amygdala and the visual cortex (Vuilleumier et al., 2004), with further processing modulated by connections with the prefrontal cortex (Ghashghaei et al., 2007). Both, the visual and prefrontal cortices have been associated with emotional face processing (Fusar-Poli et al., 2009). These findings suggest that the influence of the amygdala on behaviour in response to emotional stimuli can be mediated by both the visual and prefrontal cortex.

Functional neuroimaging studies have found that emotion regulation strategies, including reappraisal (intentional) or labelling (incidental) rely to some extent on cognitive processes (Hariri et al., 2000; Ochsner et al., 2002). Regardless of the strategy employed, regulation of emotional responses engages prefrontal cortical regions (lateral regions projecting to the medial cortex) that modulate activity in emotional response-related regions such as the amygdala (Lieberman et al., 2007; Ochsner et al., 2002; Wager et al., 2008), with recent research having confirmed a direct overlap of those neural substrates (Burklund et al., 2014; Payer et al., 2012). Structural and functional alterations in those brain regions implicated in emotion processing and regulation have previously been shown in patients with MA dependence and MAP (Aoki et al., 2013; Kim et al., 2006; Nakama et al., 2011; Orikabe et al., 2011; Schwartz et al., 2010). However, it has not yet been fully established, if MA dependence with and without a history of psychosis is associated with aberrant regulation of neural responses to affective stimuli.

In the current study, we used functional magnetic resonance imaging (fMRI) to examine deficits in neural processes underlying affect regulation in MA dependence and MAP. We employed an affect labelling task wherein participants either passively observe emotionally expressive faces or label them according to the emotion displayed. The observe condition requires automatic processing of emotional facial expressions, while labelling engages higher cognitive processes. This task has been shown to produce reliable amygdala activation in healthy individuals during the observe condition, and to emulate neural activation patterns of affect regulation during the labelling condition, i.e. an increase in right ventrolateral prefrontal cortex (VLPFC) activity and a reduction in amygdala activity (Hariri et al., 2000; Lieberman et al., 2007). Previous neuroimaging studies have employed a similar task, including an emotion labelling and emotion matching condition, in MA dependence (Payer et al., 2011), but did not detect abnormal PFC recruitment and amygdala activity modulation during emotion labelling, compared to healthy controls. However, neural substrates of affect regulation abilities have not yet been assessed in patients with MAP. Research in schizophrenia patients so far has indicated a deficient amygdala activity during emotion matching, while neural activation during affect labelling was comparable to that in healthy controls (Fakra et al., 2008). The present study sought to investigate functional brain deficits in the PFC-amygdala circuit during affect labelling; in particular, we hypothesized a reduced VLPFC activity and consequent modulatory deficits on amygdala activation in participants with MA dependence and MAP, compared to healthy controls.

Further, we predicted a decreased amygdala activity in MAP patients compared to MA-dependent individuals and healthy controls during automatic emotion processing.

6.2. Methods

6.2.1. Participants

Three groups of participants were included in this fMRI study: MA-dependent individuals (MA group), MA dependants with a history of MA-associated psychosis (MAP group), and healthy control subjects (CTRL group). MA-dependent individuals were recruited from drug treatment and rehabilitation facilities, as well as psychiatric wards in Cape Town. Healthy controls came from the same communities as the MA abusers recruited through word of mouth and flyers. Sixty-four individuals between the ages of 18 and 41 were invited to take part and underwent a face to face psychiatric assessment using the SCID-I for DSM-IV-TR (First et al., 2002). Participants were excluded from the study if they presented with: 1) additional substance dependencies other than nicotine, with exception of methamphetamine for the MA and MAP group; 2) lifetime and current diagnosis of psychiatric disorders, with exception of MAP in the MAP group; 3) a history of psychosis prior to MA abuse; 4) severe renal, hepatic, pulmonary, endocrine disease 5) neurological illness or head trauma; 6) a seropositive test for HIV; 7) MRI incompatibilities or known claustrophobia; 8) left-handedness; 9) lack of English fluency. All MAP participants were on treatment with neuroleptic agents, but treatment longer than twelve weeks at the time of scanning was an additional exclusion criterion.

6.2.2. Experimental paradigm

The intrinsic regulation of neural responses to affective stimuli was assessed using a modified version of the Affect Labelling Task (Lieberman et al., 2007). The fMRI target faces were obtained from the MacBrain NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm) and consisted of full-colour, whole-face emotional expressions (Tottenham et al., 2009). See Figure 6.1 for sample stimuli used in the paradigm.

Participants were asked to perform three different conditions of the task (“Observe”, “Emotion labelling”, and “Gender labelling”) while viewing target faces showing emotional expressions. In each condition, the target faces had an even gender ratio and depicted a negative emotional expression, either fear or anger. In the observe condition, participants observed a single target face without making a response. During the affect labelling condition, participants were given two emotion labels (“scared” and “angry”, or “enraged” and “fearful”) on the screen underneath the target face and were asked to choose the correct label. During the gender labelling condition the gender-appropriate name had to be chosen from a pair of names (for example, “Helen” and “Samuel”, or “Sheila” and “Allen”) shown on the screen underneath the target face. The gender labelling condition, matched for effort and stimulus complexity, serves as a control condition to preclude neural activity changes due to general effects of labelling and cognitive processing (Lieberman et al., 2007).

The target face was displayed for five seconds in every trial. Each task block contained eight trials and began with a three seconds instruction cue indicating the task. Between the blocks a fixation crosshair was displayed for twelve seconds. Participants responded via a button response box and were told to do so as fast as possible. They were also informed that the stimuli would remain on the screen for the entire five second trial even when a response was given before. The experimental paradigm included six task blocks in two runs. Between the two runs was a 30 seconds pause, during which participants were asked to remain perfectly still. Participant completed a brief test run before entering the scanner.

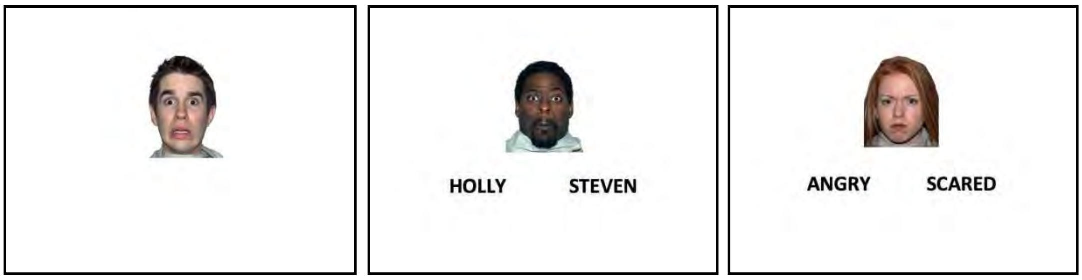


Figure 6.1. Sample stimuli from the Affect Labelling task (three conditions: Observe, Gender Labelling and Affect Labelling)

6.2.3. Image Acquisition

Images were acquired in a 3T Allegra Siemens head scanner (Siemens Medical Systems, Erlangen, Germany) using a single-channel head coil. For functional images a standard T2-weighted echo-planar imaging pulse sequence was used (TR = 3000 ms; TE = 25 ms; matrix size = 64x64; flip angle = 90°; voxel size = 3.1x3.1x3.5 mm; field of view = 200 mm, scan time = 5 min 54 s). A total of 132 volumes were obtained, each consisted of 36 interleaved slices, with slice thickness of 3.5 mm and a 5% distance factor. A high resolution multiecho MPRAGE anatomical scan was also acquired (parameters: TR = 2530 ms; graded TE = 1.53, 3.21, 4.89, 6.57 ms; flip angle = 7°; voxel size = 1x1x1 mm; field of view = 256 mm; 160 slices), allowing spatial alignment of functional images for anatomical identification.

Stimulus presentation was run by the E-Prime software tool (Schneider et al., 2002) and responses were registered by a MRI-compatible fibre optic button-box. All visual stimuli were projected onto a rear projection screen using a SANYO PLC XT-20 data projector and a specialised lens. Participants were able to see the screen through a small mirror mounted onto the head coil above their eyes.

Three data sets had to be excluded from analysis due to scanning technical deficits, additional four data sets for inadequate response behaviour by the participant, and one for excessive head movement in the scanner. The final sample comprised 56 study participants (20 MA, 16 MAP, and 20 CTRL).

6.2.4. Demographic and behavioural data analysis

Statistical analysis was performed using IBM SPSS 22 (Armonk, NY: IBM Corp). Assumption of normality of each variable was tested with the Shapiro-Wilk test. The study groups (MA, MAP, and CTRL) were compared across demographic and drug use variables using Kruskal-Wallis and chi-square tests as appropriate. For all analyses, *p*-values of < .05 were considered statistically significant.

Accuracy of performance (i.e. giving the target face the correct gender or emotion label) and response times for both labelling conditions were recorded within E-Prime and analysed in SPSS. The proportion of accurate responses was assessed within-group using Wilcoxon's signed-rank test, and between group using Kruskal-Wallis H test and Mann-Whitney U test. Response times were, after a logarithm transformation of data to achieve normal distribution, entered into a mixed-effects analysis of variance model to assess differences between and within groups. Missed responses and those given quicker than 500 ms after stimulus presentation (as they were more likely carried over from the previous trial than presenting a genuine response) were excluded from analysis.

6.2.5. Functional MRI data analysis

Spatial pre-processing

Acquired fMRI data were pre-processed and analyzed in SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk). To correct data for motion-related artefacts, functional images were realigned to the mean image of the time series, using a least squares approach and a six parameter rigid body transformation (Friston et al., 1995). Motion parameters were set to a maximum of 3 mm translation and movement beyond was exclusionary (one participant). The mean of the motion-corrected images as well as the realigned T2 images of each participant were then coregistered to the individual's anatomical T1 image, using rigid body transformation. Every participant's anatomical image has previously been manually aligned to the anterior commissure - posterior commissure line. During the following segmentation, structural T1 images were segmented into grey and white matter probability maps (Ashburner & Friston, 1997). Resulting images were further used to calculate spatial normalization parameters to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain (average scan of 152 participants, provided by SPM8), using a full affine transformation and non-linear deformations. Parameters were subsequently applied for normalisation of T2 images. To increase signal-to-noise ratio as well as inter-subject overlap all functional images were smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel. A final data quality assessment was done using the volume artefact programme of the ArtRepair software (Mazaika et al., 2007). Outliers with regards to mean intensity and scan-to-scan motion were automatically detected and repaired using linear interpolation from the nearest unrepaired slices.

Neural response analysis

First, for each participant a separate general linear model was specified, modelling the entire experiment as epochs defined by task onsets and durations, convolved with a canonical hemodynamic response function. The time series in each voxel were high-pass filtered at 1/128 Hz to remove low-frequency confounds. Realignment parameters were entered in the design matrix as nuisance regressors to reduce motion-related artefacts. Once the model has been fitted onto the data, planned comparisons of task conditions were computed for each participant at each voxel. Using a t-statistic, linear contrasts of interest were generated to investigate neural response during the observe condition compared to crosshair fixation, and during the emotion labelling condition compared to gender labelling. Contrast images were then entered into a second-level random effects full factorial analysis with age, gender, and total matter volume as covariates of no interest. Summary statistical maps of main effects and interaction of group and condition were familywise error (FWE) corrected for multiple comparisons at a set level of $p < .05$.

Given the established amygdala activation during emotion processing as well as increased right VLPFC and reduced amygdala activation during emotion labelling (Creswell et al., 2007; Liebermann et al., 2007), we first examined BOLD signal in those structures for group differences. A small volume correction (SVC) instead of a functionally defined region of interest approach was chosen to avoid circularity in the analysis (Kriegeskorte et al., 2009). Masks of bilateral amygdala and bilateral VLPFC, built with the SPM8 WFU_PickAtlas toolbox (Maldjian et al., 2003, 2004) and the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) were used. The mask for the VLPFC included the orbital, opercular, and triangular parts of the inferior frontal gyrus. For visualisation purposes, parameter estimates (beta values), averaged across all voxels within the amygdala, were extracted for each condition of the task (observe, emotion labelling, and gender labelling relative to crosshair fixation) using the MarsBaR toolbox (Brett et al., 2002), and further analysed in SPSS.

Between-group effects of task-related neural activation were further investigated in whole-brain analyses, performing two-sample *t*-tests, respectively. To allow replication of results from previous studies using this task, clusters of active voxels from group comparisons were identified at an uncorrected p-value of .005 combined with a cluster size threshold of 10. There is the possibility of an unquantified control of Type I errors at this threshold, but Lieberman and Cunningham (2009) have demonstrated that the threshold produces appropriate Type I and II error rates. Neural response coordinates are reported in MNI space (x = sagittal plane, y = coronal plane, z = axial plane) and results were explored for corresponding brain regions using WFU_PickAtlas toolbox and the AAL atlas (Tzourio-Mazoyer et al., 2002).

Lastly, the association of brain activity during emotion labelling with MA use measures (duration of abstinence, duration of use, and age at first use) was assessed within the MA and MAP groups. In addition, the association with symptoms (PANSS scores) and duration of antipsychotic medication was examined in the MAP group. Therefore, multiple regression analyses were conducted for the emotion labelling versus gender labelling contrast, with age, gender, and total matter volume as covariates of no interest. The threshold for statistical maps was set at an uncorrected p-value of .001 combined with a cluster size threshold of 50 to correct for multiple comparisons and to reduce diffusivity of the signal in this analysis.

6.3. Results

6.3.1. Demographics and Substance Use

Demographic and clinical characteristics of the three study groups are summarized in Table 6.1. Statistical analysis revealed no significant differences between groups in age and gender distribution. However, healthy controls showed higher levels of education compared to the MA group, $U = 102.5$, $p = .007$, and MAP group, $U = 36.5$, $p < .001$. Across both MA-dependent groups, participants did not differ in MA use variables (i.e. duration and onset of use, and duration of abstinence) or in non-MA drug use variables. However, in the CTRL group numbers of tobacco smokers were significantly lower compared to MA, $\chi^2(1) = 4.286$, $p = .038$, and MAP groups, $\chi^2(1) = 4.425$, $p = .035$. Also, the MAP group used significantly more methaqualone in the last year in comparison to the CTRL group, $\chi^2(1) = 11.683$, $p = .001$.

Table 6.1. Demographic characteristics and clinical information for MA-dependent individuals with and without a history of psychosis and healthy controls

Demographic Measures	MA n=20	MAP n=16	CTRL n=20	test for group difference
male/female, n	17/3	14/2	17/3	$\chi^2(2)=.058$, $p= .971$
Age in years, median (range)	25 (19-30)	22.5 (18-41)	23.5 (18-38)	$H(2)=.138$, $p= .933$
Level Of Education in years, median (range)	10 (8-15)	9.5 (8-13)	12 (9-14)	$H(2)=16.35$, $p< .001$
Tobacco smokers in last year, n	17	14	11	$\chi^2(2)=6.667$, $p= .036$
Alcohol consumers in last year, n	12	12	11	$\chi^2(2)=1.60$, $p= .449$
Cannabis users in last year, n	12	9	8	$\chi^2(2)=1.781$, $p= .410$
Methaqualone users in last year, n	5	9	1	$\chi^2(2)=11.956$, $p=.003$
Total Matter Volume in ml, mean (SD)	1175.3 (108.7)	1185.6 (124.8)	1166.9 (111.9)	$F(2,53)=.117$, $p= .890$
MA Use Measures				
Age at first use in years, median (range)	18 (12-27)	17.5 (12-40)		$U= 153.5$, $p= .835$
Duration in years, mean±SD (range)	5.7±2.3 (1.5-10)	5.5±3.2 (1-12)		$t(34)= .226$, $p= .823$
Abstinence in days, median (range)	28 (1-240)	46.5 (1-270)		$U= 124.0$, $p= .251$
Clinical Measures				
Neuroleptic Medication in days, M±SD (range)		44.3±19.7 (14-85)		
PANSS negative symptoms, median (range)		11 (7-37)		
PANSS positive symptoms, median (range)		10 (7-24)		
PANSS psychopathology, median (range)		26.5 (16-42)		

PANSS: Positive and Negative Syndrome Scale. M: mean, SD: standard deviation.

6.3.2. Behavioural Responses

The mixed effects model for response time revealed a main effect of study group, $F(2,1510.1) = 142.8$, $p < .001$ and task condition, $F(1,1510.4) = 140.5$, $p < .001$, and an interaction between study group and task condition, $F(2,1510.1) = 5.1$, $p = .006$. Mean behavioural responses and pairwise group comparisons (Sidak corrected) are shown in Table 6.2. When comparing response times between task conditions, each group showed significantly slower responses for the emotion labelling condition (MA: $t = -9.62$, $p = .001$, $d = -0.67$, MAP: $t = -4.55$, $p = .001$, $d = -0.36$; CTRL: $t = -8.35$, $p = .001$, $d = -0.52$).

Also, performance accuracy differed significantly between the three groups for the emotion labelling condition, $H(2) = 14.14$, $p < .001$; see Table 6.2 for group comparisons. There was no significant difference in accuracy for the gender labelling condition, $H(2) = 5.6$, $p = .061$. Within each group, accuracy in emotion labelling was significantly reduced compared to accuracy in gender labelling (MA: $z = -2.997$, $p = .003$, $d = -0.73$, MAP: $z = -3.114$, $p = .002$, $d = -0.89$; CTRL: $z = -2.871$, $p = .004$, $d = -0.42$).

Table 6.2. Mean behavioural scores and group differences for response time and accuracy during emotion and gender labelling conditions

				Group comparisons								
	MA	MAP	CTRL	MA-CTRL			MAP-CTRL			MA-MAP		
	M ± SD	M ± SD	M ± SD	*U*	*p*	*d*	*U*	*p*	*d*	*U*	*p*	*d*
Accuracy												
Emotion labelling	0.89 ± 0.13	0.73 ± 0.18	0.92 ± 0.11	165.5	0.338	-0.25	54.0	.001	-1.27	66.0	.003	1.02
Gender labelling	0.96 ± 0.04	0.87 ± 0.13	0.96 ± 0.08									
Reaction time in s												
Emotion labelling	2.27 ± 0.79	2.68 ± 0.88	1.97 ± 0.6		<.001	0.43		<.001	0.94		<.001	-0.49
Gender labelling	1.78 ± 0.66	2.36 ± 0.91	1.65 ± 0.64		.049	0.2		<.001	0.9		<.001	-0.73

M: mean, SD: standard deviation, Cohen’s d: effect size, s: seconds.

6.3.3. A priori brain regions analyses

To test our hypothesis of amygdala dysfunction in MAP and VLPFC dysfunction in both clinical groups we conducted SVC analyses in those regions for the contrasts observe condition relative to crosshair fixation, and emotion labelling condition relative to gender labelling. Replicating previous findings, bilateral amygdala activation during the viewing of faces displaying negative emotions was shown for healthy controls (left: -24, -6, -12; $z = 4.15$; 134 voxels; right: 32, -4, -14; $z = 4.14$; 146 voxels). Additionally, the MAP group displayed right amygdala activation (32, 4, -20; $z = 2.98$; 19 voxels). Although the within-group analysis revealed no statistically significant amygdala activation in the MA group for this contrast, no group differences were found between CTRL and MA groups, indicating similar activity pattern in the two groups (see Table 6.3 and Figure 6.2). The MAP group, however, showed reduced activation of the left amygdala, compared to the CTRL and MA groups. During emotion labelling, the MA group yielded greater activation of the left amygdala relative to healthy controls (one voxel only).

For visualisation purposes, intensity values (parameter estimates) from the anatomically defined bilateral amygdala were extracted from each participant. As activation values from left and right amygdala showed strong correlations for the three task conditions (all $r > 0.77$, all $p < .001$), bilateral measures were combined to an average ROI. Figure 6.2 shows bilateral amygdala activation during the three conditions of the task relative to crosshair fixation as well as for the two contrasts of emotion labelling relative to the observe condition and to the gender labelling condition, for the three study groups. Multivariate analysis of variance revealed a significant main effect of condition, $F(2,52) = 4.38$, $p = .018$. Follow-up t-tests showed that across participants, amygdala activity was reduced during the emotion labelling condition, $t(55) = -2.91$, $p = .005$, but not during the gender labelling condition, $t(55) = -.65$, $p = .517$. Despite Figure 6.2 indicating overall reduced amygdala responsivity in the MAP group relative to MA and CTRL groups, no main effect of group was found.

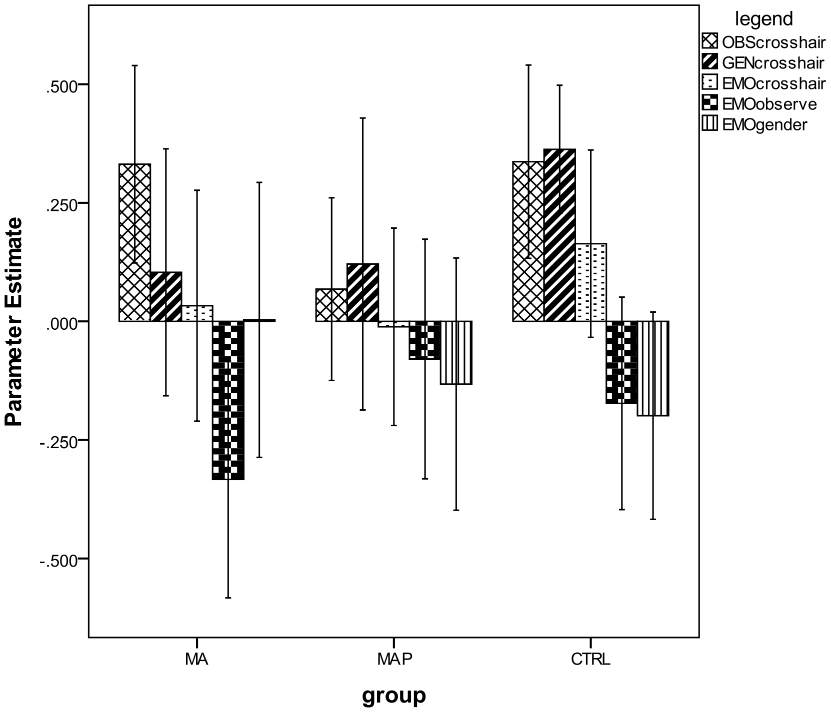


Figure 6.2. Mean bilateral amygdala activation for the three task conditions observe (OBS), gender labelling (GEN), and emotion labelling (EMO) versus crosshair fixation as well as for the two contrasts of emotion labelling versus observe and gender labelling for each of the three study groups.

Affect labelling resulted in increased left VLPFC activity in the MA group, compared to the CTRL and MAP group (see Table 6.3), with no differences for right VLPFC activation. In contrast, the MAP group showed diminished right VLPFC activation during emotion labelling, compared to CTRLs (three voxels only).

Table 6.3. Task-related differential activity in a priori defined regions: between-groups analysis for MA-dependent individuals with and without a history of psychosis and healthy controls

	Laterality	cluster size	MNI coordinates x	y	z	Z-score
Observe condition relative to crosshair fixation						
CTRL > MA						
VLPFC	R	13	32	6	34	3.39
	R	6	50	20	38	2.81
CTRL > MAP						
VLPFC	L	432	-44	30	2	3.85
	R	131	42	24	-8	3.65
	R	12	36	12	30	2.72
Amygdala	L	4	-24	0	-12	2.79
MA > MAP						
VLPFC	L	436	-44	24	0	4.64
	R	11	54	32	-8	3.32
	R	28	50	18	-6	3.30
	R	19	40	26	-14	3.08
Amygdala	L	1	-24	0	-12	2.79
Emotion labelling relative to Gender labelling condition						
MA > CTRL						
VLPFC	L	81	-50	44	0	3.29
Amygdala	L	1	-18	0	-12	2.82
CTRL > MAP						
VLPFC	R	2	40	22	-20	3.04
	R	1	52	8	20	2.59
MA > MAP						
VLPFC	L	101	-52	28	6	3.14
	R	7	54	40	4	2.95
	L	14	-56	12	28	2.79

Significant clusters at peak-level after small volume correction (uncorrected $p < .005$) are shown for contrasts of interest in a priori defined regions. Laterality: L=Left, R=Right. VLPFC: ventrolateral prefrontal cortex.

6.3.4. Whole-brain analysis results

The random effects full factorial analysis revealed no main effect of group, but a main effect of condition and the group by condition interaction, as shown in Table 6.4. Post-hoc within-group analysis replicated the earlier SVC finding of amygdala activation (-26, -8, -10; $z = 4.31$, as part of a bigger cluster of 676 voxels stretching over the globus pallidus and parahippocampal gyrus) during the observe condition for the CTRL group. One cluster of significant activation was revealed for the left middle frontal gyrus (-38, 14, 52; $z = 2.86$; 10 voxels) during the labelling condition in this group.

Differences of neural responses between the three study groups during the observe condition can be seen in Table 6.5. In comparison to healthy controls, the MA group showed reduced activation in frontal regulatory brain regions, the cuneus, precuneus and the caudate, while showing increased activation in the visual cortex. For the MAP group, a reduced activation in the cerebellum, striatum, insula, superior temporal and inferior frontal gyrus, and supplementary motor area was found, while increased neural response was primarily shown for the somatosensory and visual cortex as well as the middle temporal and middle frontal gyrus, relative to the CTRL group. Comparison of the two MA-dependent groups indicated that in the MAP group there was reduced activation in occipital and temporal cortices, the striatum, insula, cerebellum, and thalamus.

Table 6.4. Random effects full factorial results

	Laterality	cluster size	MNI coordinates x	y	z	Z-score
Main effect of group						
no suprathreshold clusters						
Main effect of condition contrasts						
Middle occipital gyrus	L+R	14407	-22	-98	2	>8
Medial fronto-orbital gyrus	R	196	4	24	-14	7.57
Middle frontal gyrus, Pars orbitalis	L	155	-38	44	-2	6.51
Inferior frontal gyrus, Pars triangularis	R	71	56	30	-2	6.01
Inferior frontal gyrus, Pars orbitalis	L	61	-54	26	-4	5.90
Middle temporal gyrus	L	46	-62	-6	-10	5.77
Angular gyrus	R	122	46	-72	34	5.66
Superior temporal gyrus	R	46	54	0	-2	5.44
Inferior frontal gyrus, Pars triangularis	L	30	-54	20	30	5.42
Middle frontal gyrus	R	71	28	26	48	5.40
Postcentral gyrus	R	10	46	-22	38	5.36
Supplementary motor area	L	34	-2	0	62	5.28
Rolandic operculum	R	17	44	-32	20	5.26
Parahippocampal gyrus	R	11	24	-18	-24	5.24
Rolandic operculum	L	35	-40	-32	16	5.09
Superior temporal gyrus	L	13	-60	-30	16	5.05
Fusiform gyrus	R	11	26	-30	-22	5.00
Group x condition interaction						
Middle occipital gyrus	L+R	12078	-22	-98	2	4.51
Inferior occipital gyrus	L		-36	-82	-12	4.29
Medial orbital gyrus	R	126	4	24	-14	7.16
Middle frontal gyrus, Pars orbitalis	L	89	-38	44	-2	6.07
Inferior frontal gyrus, Pars orbitalis	L	35	-54	24	-4	5.67
Inferior frontal gyrus, Pars triangularis	L		-58	24	6	4.93
Inferior frontal gyrus, Pars triangularis	R	44	56	30	-2	5.64
Middle temporal gyrus	L	12	-62	-6	-10	5.27
Angular gyrus	R	43	46	-72	34	5.25
Parahippocampal gyrus	R	17	16	-28	-14	5.22
Middle frontal gyrus	R	16	28	26	48	4.93

Significant clusters for main effects and interaction shown (FWE corrected, p<.05, extent threshold=10) are shown. The anatomical areas defined in the Automatic Anatomical Labelling (AAL) atlas are listed for each cluster, ordered by decreasing statistical significance. Z-score, p-values and MNI coordinates refer to the voxel with the peak value. Laterality: L=Left, R=Right.

Table 6.5. Between-group differences in brain regions showing task-related activity during observe condition compared to crosshair

	Laterality	cluster size	MNI coordinates x	y	z	Z-score
CTRL > MA						
Middle frontal gyrus	R	20	32	8	36	3.67
Cuneus	R	66	20	-58	34	3.34
Precuneus	R	31	10	-50	44	3.28
Parahippocampal gyrus	L	14	-18	-12	-26	3.24
Middle frontal gyrus	R	34	48	20	38	3.17
Supplementary motor area	R	10	10	18	52	3.07
Precentral gyrus	L	11	-34	-14	58	3.04
Caudate nucleus	L	20	-12	22	-8	3.01
MA > CTRL						
Inferior occipital gyrus	R	40	46	-78	-4	3.64
Middle occipital gyrus	L	25	-38	-86	4	3.22
CTRL > MAP*						
Cerebellum, Anterior lobe	L	1322	-10	-42	-34	4.85
Globus Pallidus	R	186	18	6	-4	4.16
Putamen			24	10	-8	4.06
Insula	R	496	46	10	-10	4.00
Inferior frontal gyrus, Pars triangularis	L	885	-44	30	2	3.85
Parahippocampal gyrus	L	58	-18	-10	-28	3.81
Supplementary motor area	L	244	-4	18	60	3.71
Cerebellum, Vermis_4_5	R	72	4	-62	-2	3.32
Superior temporal gyrus	R	266	56	-38	8	3.25
MAP > CTRL						
Postcentral gyrus	L	100	-40	-44	62	3.84
Postcentral gyrus	R	139	54	-22	42	3.72
Middle occipital gyrus	R	69	-30	-74	38	3.54
Middle temporal gyrus	L	31	-48	-50	-6	3.28
Precentral gyrus	L	31	-56	10	34	3.27
Superior parietal lobule	L	44	-16	-64	48	3.06
Middle frontal gyrus	L	11	-28	4	64	3.04
MA > MAP*						
Inferior occipital gyrus	R	106	44	-78	-2	4.25
Superior temporal pole	L	754	-48	20	-14	4.01
Thalamus	L	140	-4	-20	8	3.98
Precentral gyrus	R	223	14	-28	72	3.97
Angular gyrus	L	57	-48	-76	26	3.67
Putamen	L	151	-26	-8	-8	3.65
Putamen	R	201	30	0	2	3.62
Middle temporal gyrus	R	140	56	-64	10	3.59
Superior temporal gyrus	R	131	50	-28	0	3.39
Insula	R	140	46	14	-8	3.34
Cerebellum, Vermis_6	R	105	2	-70	-14	3.33

Cerebellum_6	L	140	-36	-66	-22	3.25
Cerebellum, Vermis_9	R	145	2	-54	-30	3.25
Middle occipital gyrus	L	54	-34	-90	12	3.19
Supplementary motor area	R	102	6	22	62	3.10
MAP > MA						
Paracentral lobule	L	13	-10	-28	52	3.34
Caudate nucleus	R	11	8	12	-10	3.20
Inferior parietal lobule	L	19	-46	-36	50	2.90

Significant clusters at peak-level (uncorrected *p*<.005, extent threshold=10, *marked CTRL>MAP and MA>MAP group comparison: extent threshold=50) are shown for the observe condition versus crosshair. The anatomical areas defined in the Automatic Anatomical Labelling (AAL) atlas are listed for each cluster, ordered by decreasing statistical significance. Laterality: L=Left, R=Right.

Between-group differences for emotion labelling versus gender labelling contrast are shown in Table 6.6. The MA group showed no reduced neuronal response in comparison to healthy controls, but demonstrated significantly increased activity in occipital and temporal areas, the cerebellum, and inferior frontal gyrus. In the MAP group, compared to CTRLs, increased activity was found for the visual cortex and the parahippocampal gyrus, while smaller clusters in the rolandic operculum, posterior cingulate gyrus and superior frontal gyrus demonstrated reduced activity. Relative to the MA group, MAP participants showed reduced activation in the postcentral, inferior temporal and inferior frontal gyri, and the caudate.

6.3.5. Relationship of neural responses with MA use and clinical features

Table 6.7 shows results from regression analyses with MA use duration, psychotic symptoms, and medication duration in the MAP group. During emotion labelling compared to gender labelling, PANSS negative symptoms scores were associated with greater activity in frontal cortical areas of the emotion regulation circuitry, including the anterior cingulate cortex, inferior frontal gyrus, and the caudate. PANSS positive symptoms scores, however, were associated with greater activity in temporal brain regions, the insula, cuneus, and angular gyrus. Longer duration of MA use was associated with greater activity in the frontal cortex, posterior temporal and parietal brain regions. Finally, duration of antipsychotic medication showed a positive association with activity in motor areas. No negative associations were found in this series of regression analyses. Also, no association of neural activity during emotion labelling with MA use measures was found in the MA group.

Table 6.6. Between-group differences in brain regions showing task-related activity during emotion labelling condition compared to gender labelling

	Laterality	cluster size	MNI coordinates x	y	z	Z-score
CTRL > MA						
no suprathreshold clusters						
MA > CTRL*						
Calcarine sulcus	R	222	18	-70	10	3.49
Middle temporal gyrus	L	54	-56	-56	16	3.41
Inferior temporal gyrus	L	55	-46	-54	-14	3.36
Cerebellum_4_5	R	54	16	-42	-20	3.19
Inferior frontal gyrus, Pars triangularis	L	86	-50	44	0	3.05
CTRL > MAP						
Rolandic operculum	L	11	-50	-8	14	3.11
Posterior cingulate gyrus	R	21	2	-14	26	3.09
Superior frontal gyrus	L	15	-18	4	54	2.90
MAP > CTRL						
Superior occipital gyrus	L	36	-12	-100	10	3.59
Lingual gyrus	R	192	12	-74	2	3.36
Parahippocampal gyrus	L	28	-26	-52	0	3.06
MA > MAP*						
Postcentral gyrus	R	148	34	-22	46	3.70
Caudate nucleus	R	114	10	6	16	3.50
Inferior temporal gyrus	L	66	-46	-56	-14	3.15
Inferior frontal gyrus, Pars triangularis	L	101	-52	28	6	3.14
Postcentral gyrus	L	103	-56	-8	38	2.97
MAP > MA						
no suprathreshold clusters						

Significant clusters at peak-level (uncorrected *p*<.005, extent threshold=10, *MA>CTRL and MA>MAP group during emotion labelling: extent threshold=50) are shown for the emotion labelling condition compared to the gender labelling condition. The anatomical areas defined in the Automatic Anatomical Labelling (AAL) atlas are listed for each cluster, ordered by decreasing statistical significance. Laterality: L=Left, R=Right.

Table 6.7. Neural activity positively associated with psychotic symptoms and duration of MA use during intrinsic emotion regulation in MA-dependent individuals with a history of psychosis

	Laterality	cluster size	MNI coordinates x	y	z	Z-score
PANSS negative symptoms						
Inferior frontal gyrus, Pars triangularis	R	122	50	36	0	4.15
Middle frontal gyrus	R		50	46	4	3.85
Anterior cingulate cortex	R	82	6	26	-6	4.04
Caudate nucleus	R		10	20	-2	3.93
Anterior cingulate cortex	L	63	-4	32	14	3.48
PANSS positive symptoms						
Middle temporal gyrus	R	67	48	-56	16	4.56
			54	-72	14	4.07
Insula	L	138	-40	-12	2	4.08
Middle temporal gyrus	L		-60	-10	-6	3.85
			-66	-14	-12	3.61
Cuneus	L	88	-4	-74	32	4.04
			-12	-74	30	3.15
Rolandic operculum	L	61	-44	-32	20	3.83
Superior temporal gyrus	R	53	64	-6	2	3.64
Heschl gyrus	R		56	-4	6	3.24
Angular gyrus	L	50	-44	-64	32	3.63
			-38	-70	40	3.33
Antipsychotic medication						
Cerebellum, Anterior lobe	R	116	14	-48	-36	4.21
Supplementary motor area	L	104	0	24	60	3.93
MA use duration						
Anterior cingulate cortex	L	299	-8	44	-4	4.40
Medial orbital gyrus	L		-2	50	-6	4.17
Angular gyrus	L	59	-38	-56	34	3.59
Middle temporal gyrus	L		-40	-58	20	3.55
Posterior cingulate cortex	R	76	2	-50	28	3.56
Precuneus	R		2	-64	26	3.31
Cuneus	L		-6	-74	26	3.27

Significant clusters at peak-level (uncorrected $p<.001$, extent threshold=50) are shown for the emotion labelling versus gender labelling contrast. The anatomical areas defined in the Automatic Anatomical Labelling (AAL) atlas are listed for each cluster, ordered by decreasing statistical significance. Laterality: L=Left, R=Right. MA=methamphetamine.

6.4. Discussion

We examined brain function during automatic processing as well as incidental regulation of affect in MA, MAP and CTRL groups, using an established affect labelling task known to activate amygdala and prefrontal cortex regions. The main findings of the current study were 1) the extent of amygdala activation during the automatic observe condition was reduced in the MAP group compared to the other groups, while affect labelling produced similar amygdala activation patterns in MA, MAP, and CTRL groups; 2) VLPFC activity was reduced in MAP and MA relative to CTRL group during the automatic observe condition, while the MA group showed VLPFC hyperactivity relative to MAP and CTRL groups during affect labelling. Whole brain analyses further revealed that MA participants showed hyperactivity in primary visual and lateral temporal face recognition areas during affect labelling relative to CTRLs, whereas MAP patients showed increased recruitment of the visual cortex and medial temporal brain areas.

When asked to observe angry and fearful faces, control participants demonstrated stable bilateral amygdala activation, as usually evoked during emotion perception (Hariri et al., 2000; Lieberman et al., 2007). Consistent with our prediction, the MAP group showed reduced amygdala activity during automatic emotion processing, which converges with findings from schizophrenia research (Fakra et al., 2008; Taylor et al., 2012). This finding of amygdala dysfunction adds to previously reported structural grey matter deficits (Orikabe et al., 2011), i.e. reduced amygdala volumes, in MAP patients. The MAP group further demonstrated a bilateral reduction in VLPFC activation. Together, this frontolimbic hypoactivation during emotional face processing suggests a diminished emotional salience attribution to the stimuli and emphasizes the potential importance of aberrant emotional perception in the pathogenesis of MAP. In the MA group, activation in the right VLPFC was reduced during automatic emotion processing, which has previously been attributed to poor emotional insight and consequently increased aggression in this population (Payer et al., 2011).

Contrary to our hypothesis, MAP patients did not differ from the CTRL group in amygdala activity. The MA group showed a slight activity increase in one voxel of the left amygdala. Similar amygdala activity during the affect labelling condition suggests that all three study groups achieved an effective and comparable amygdala inhibition during intrinsic affect regulation. However, the finding is in keeping with previous research in schizophrenia and MA dependence, where patients showed similar amygdala activation patterns as healthy controls during an emotional labelling task (Fakra et al., 2008; Payer et al., 2012). There is emerging evidence from neuroimaging studies that the VLPFC provides a ‘top-down’ modulation of amygdala activation during affect labelling (Creswell et al., 2007; Hariri et al., 2000; Lieberman et al., 2007). In the present study, MA participants relative to healthy controls showed hyperactivation of the left VLPFC during the cognitive evaluation of affective stimuli in the labelling condition. This might be indicative of successful compensatory activation of prefrontal control areas in the left hemisphere to meet task-related cognitive demands and sufficiently regulate affect. The MAP group of the present study, however, displayed reduced activation in small clusters of the right VLPFC relative to healthy controls and MA participants, reflecting a diminished cognitive engagement during the emotion labelling. Notably, a previous study of the neural mechanisms of emotion processing and labelling in MA-dependent individuals reported reduced activation of bilateral prefrontal areas when matching facial affect, but reported no deficits during affect labelling (Payer et al., 2011). Since that study compared significant clusters within the inferior frontal gyrus retrieved from a functional connectivity analysis with the amygdala a direct comparison of results is not feasible. The finding of decreased VLPFC engagement here does, however, parallel previously reported prefrontal cortex deficits in MAP patients, indicated by volume reduction (Aoki et al., 2011) and decreased neuronal integrity (Howells et al., 2014).

Results from whole-brain group comparisons indicated that both MA-dependent groups exploited significantly more processing resources in visual occipitotemporal cortices when verbally encoding emotional expressive faces. This may reflect a neural compensation during the higher task demands on processing of the facial stimuli and their labels. The MAP group demonstrated an increased engagement of the superior occipital, lingual, and parahippocampal gyrus. Research studies have previously shown that the lingual and parahippocampal gyrus, both implicated in face processing (Fusar-Poli et al., 2009), demonstrate aberrant activity during emotional processing in psychotic disorders. In schizophrenia, a hypoactivation of the parahippocampal gyrus has been associated with disturbed emotional face processing (Li et al., 2009), and in individuals at high risk for psychosis emotion discrimination was associated with hyperactivation of the lingual gyrus (Seiferth et al., 2008). Interestingly, in the MAP group, the increased occipitotemporal activation associated with emotional face processing was accompanied by a deficient recruitment of the superior frontal gyrus, rolandic operculum, and the posterior cingulate gyrus; the latter being generally activated by emotional words (Maddock et al., 2003). This might suggest that MAP patients attribute less emotional salience to the stimulus labels, which in addition to the lack of cognitive engagement indicated by reduced VLPFC activity, may potentially underlie their impaired task performance during emotion labelling (while gender labelling performance compares to that of the CTRL and MA groups).

In comparison, in the MA group, affect labelling relative to gender labelling elicited increased activity in lateral temporal brain regions responsive to faces and word meaning, and the primary visual cortex, compared to healthy controls. It has been shown that the amygdala is responsible for functional activity changes in cortical visual pathways in response to emotional stimuli (Vuilleumier et al., 2004). MA participants showed a slight increase in amygdala activity during affect labelling, potentially enhancing the perceptual analysis of the emotional stimuli in occipitotemporal regions. However, there is also growing evidence that the prefrontal cortex modulates extrastriate visual processing (Büchel & Friston, 1997), contributing to selective attention (Squire et al., 2013) and providing bias signals that can either increase or decrease representations in the visual pathways (Hillyard & Anllo-Vento, 1998). Therefore, the increased visual cortex activity might be a function of the VLPFC overactivation, potentially reflecting a biased processing of the negative task stimuli in MA. Further work is needed to confirm the hypothesis that while MAP is characterised by frontolimbic hypoactivity and reduced salience attribution during emotion processing, MA is characterised by an increased emotional evaluation and prefrontal and occipitotemporal hyperactivity during cognitive engagement with the stimuli.

As clinical symptoms may play an important influential role in neuroimaging studies, we assessed the association between MAP patient characteristics (PANSS scores) and neural activity during affect labelling while controlling for age, gender and total brain matter volume. In the present study, positive psychotic symptoms were found to be associated with increased neural activity in areas of the primary auditory and auditory association cortex, including the superior and middle temporal gyrus, and the Heschl gyrus. These areas have previously been implicated in acoustic hallucinations and thought disorder in schizophrenia patients (Lennox et al., 2000; Shenton et al., 1992). Additional areas, in which neural activity related to positive psychotic symptoms, were the insula and cuneus, both previously associated with hallucinations (Allen et al., 2008). Emerging evidence from neuroimaging research in schizophrenia has suggested an association of temporal lobe abnormalities with positive symptoms and of frontal cortex abnormalities with negative symptoms (Heckers et al., 1999). In line with this notion, we further found a relationship between negative symptoms and neural response in the inferior and middle frontal gyrus, and the anterior cingulate cortex.

A number of limitations to this study should be considered. First is the issue of generalisability of the results in terms of unequal gender distribution. Males have been shown to activate limbic and prefrontal cortical areas to a greater extent than females during emotional processing (Fusar-Poli et al., 2009). The current sample consists mainly of male participants in all three study groups and discussed results may therefore be less characteristic for females. Second, there is the possibility that some activation differences between MAP patients and controls might derive from differences in performance, which differed significantly in the emotion labelling condition. We attempted to address this confounding factor by excluding datasets where participants demonstrated a response accuracy of less than 60% (four sets in the MAP group). Further, antipsychotic medication use might be a potential limitation to the study of the neural correlates of affective labelling. However, a study in first-episode schizophrenia patients found stable cerebral dysfunctions of the cortico-limbic regions before and after therapy with antipsychotics (Reske et al., 2007). Additionally, assessment of the effects of medication duration in the MAP group revealed an association with cerebellum and supplementary motor cortex activation, possibly reflecting the medication's extra-pyramidal side effects associated with motor coordination in MAP. But no association was found with core emotional structures. Taken together, this provides strong evidence that measures of affective neural functioning here were not confounded by antipsychotic treatment.

In summary, emotion processing and regulation in MA dependence and MAP were associated with aberrant functionality in a modulatory network comprising the amygdala, prefrontal cortex and occipitotemporal areas. In MA-dependent individuals, overactivation in amygdala, VLPFC and visual cortices during affect labelling may be associated with greater bias towards negative emotional stimuli, greater cognitive engagement as well as visual attention and perception. In MAP patients, however, frontolimbic hypoactivity during automatic emotion processing suggests reduced emotional salience attribution, which together with decreased cognitive engagement and impaired facial affect identification may underlie the poor social performance reported in patients with MAP.

Chapter 7

General discussion and conclusion

The preceding four chapters have attempted to address a number of aims and specific research questions regarding the neural correlates of affect dysregulation in methamphetamine dependence with and without a history of psychosis. Although in-depth discussions have been provided for the major findings within these chapters, the final chapter will integrate the relevant findings to provide a comprehensive summary of the studies presented in this thesis. Limitations and suggestions for future research will be discussed and some final conclusions will be provided.

Summary

The aim of this project was to delineate affect regulation and social cognition abilities in individuals with MA dependence and MAP, and to determine the degree to which MA-related brain changes in structure and function differentially underpin affect dysregulation in these populations, and underpin psychotic symptoms in MAP.

On the behavioural level, we found in line with expectations, that both MA-dependent groups demonstrated impaired abilities in social cognition, as evidenced by poor performance in the emotion recognition task and the reading the mind in the eyes task. As the reliable discrimination of emotional expressions in faces is essential for adequate social interaction, it has previously been suggested that social-cognitive difficulties may contribute to the social behavioural abnormalities associated with MA use (Homer et al., 2008). Further, social cognition capacities were impaired to a greater extent in the MAP group relative to MA group. In particular, while emotion recognition abilities were selectively impaired for the recognition of anger in the MA group, a generalised impairment for anger, fear, happiness, and sadness recognition was observed in MAP participants. In agreement with our second hypothesis of this study, we found that relative to healthy controls both MA-dependent groups showed increased levels of aggression; however, against our prediction, aggression levels were comparable between both groups. This could possibly be ascribed to the fact that antipsychotic medication in the MAP group lowered symptom severity of self-report aggression. Contrary to our initial hypothesis that affect dysregulation would be associated with impaired social cognitive functioning, we did not detect such association, suggesting a potentially independent disturbance of the two phenomena in individuals who are dependent on MA with and without a history of psychosis. Taken together, the reported increased levels of aggression and impaired social cognition capacities support the notion of MA-dependent individuals having problems to retain their social graces and interpersonal relationships. Particularly in the MAP group, inadequate social interaction may be ascribed to an unreliable discrimination of emotions displayed by others. Further, the reported behavioural impairments may not only relate to negative social outcome, but also adversely impact treatment success (Rawson et al., 2002).

Additional support for impaired affect regulation in MA and MAP was provided by the finding of higher scores on the difficulties in emotion regulation scale as well as the emotion reactivity scale in both groups. The structural MRI study presented in this thesis further demonstrated cortical thinning in the left pars triangularis of the inferior frontal gyrus and reduced hippocampal volumes in MAP participants relative to healthy controls. In direct comparison of the two MA-dependent groups, MAP participants relative to the MA group showed cortical thinning in the left fusiform, inferior temporal, lateral and medial orbitofrontal, pars orbitalis and triangularis, and the insular cortex, in addition to hippocampus volume reductions. These findings suggest that loss of cortical and subcortical grey matter in MAP may reflect underlying neuropathological abnormalities as seen in other psychiatric disorders such as schizophrenia (Kuperberg et al., 2003; Nesvåg et al., 2008); and may underpin the social and behavioural problems in MAP, given the role those prefrontal and temporal structures play in affect regulation, aggression, and the promotion of socio-emotional processes such as face perception (Davidson et al., 2000; Kohn et al., 2014; Haxby et al., 2000). This argument is further supported by the fact that, in line with our hypothesis, cortical thinning in the PFC and inferior temporal gyrus was associated with higher levels of self-report emotional reactivity and difficulties in the ability to regulate emotions in the MAP group.

We could not confirm our hypothesis of cortical thinning in frontotemporal brain regions in the MA group, but instead found greater cortical thickness in the entorhinal and insular cortex, compared to healthy controls. While the entorhinal cortex is part of a network mediating learning and memory (Squire & Zola-Morgan, 1991), the insula has been implicated in emotion regulation, emotional awareness and empathy (Bernhardt & Singer, 2012; Davidson et al., 2000), processes reported to be dysfunctional in drug addiction. The increase of cortical thickness may point to inflammatory or microgliosis processes, previously hypothesized to underlie brain volume increases observed in MA dependence (Chang et al., 2005; Jernigan et al., 2005), or alternatively represent the stimulation of brain neurotrophic agents such as BDNF (Kim et al., 2005). Further, hypothesised volumetric grey matter changes in the basal ganglia were not found in this study; however, previous research findings of volumetric changes in subcortical regions have proven to be inconsistent (Schwartz et al., 2010). This could possibly be ascribed to methodological differences, but also variability in sample characteristics such as duration of abstinence from MA. Nevertheless, the pathophysiology of cortical volume or thickness decrease and increases is still unclear, and further work is needed to understand the underlying neurobiology.

In the DTI study we showed diminished white mater integrity in the internal capsule and frontal projection fibres in the MA group, further substantiating the notion of corticostriatal alterations in MA as supported by a growing body of literature of various scan modalities (London et al., 2014). The finding of higher mean diffusivity in those white matter tracts may, again, suggest inflammatory processes or myelin loss (Alexander et al., 2007). In keeping with our hypothesis, white matter changes, evidenced by increased diffusivity and decreased FA, were far more widespread in the MAP group relative to healthy controls and MA participants. Similar general disorganisation of white matter structure has been reported in schizophrenia (Kubicki et al., 2007), and there is growing evidence for oligodendrocyte death and demyelination to underlie these changes due to the oligodendrocytes' sensitivity to glutamate-induced neurotoxicity (McDonald et al., 1998). Evidence of enhanced glutamate signalling in MAP (Hsieh et al., 2014) and MA-induced cytotoxicity in oligodendrocytes (Genc et al., 2003), support the notion of similar degenerative pathophysiological processes in MAP. Consistent with a view of white matter pathology contributing to problems in impulse control (Lim et al., 2008; Moeller et al., 2005), I found frontal white matter damage (in the anterior corona radiata) to be related with higher levels of self-report impulsivity in the MAP group. However, contrary to my hypothesis, I did not find such an association in the MA group. The lack of significant associations between structural deficits and behavioural data in the MA group may be attributed to the possibility that MA-related effects are subthreshold to statistical significance, while in the MAP group the effect size is higher, indicative of greater brain damage.

Assessment of cortical and amygdalar activity during emotion perception and emotion labelling in the fMRI study found a frontolimbic hypoactivation during the passive viewing of emotional faces in the MAP group, suggesting a diminished emotional salience attribution to the stimuli. This finding, in addition to the previously discussed emotion recognition deficits, suggests the potential importance of aberrant emotional perception in the pathogenesis of MAP. The MA group, to a lesser extent, demonstrated decreased activation of the VLPFC during emotion processing, which has previously been attributed to poor emotional insight and consequently increased aggression in this population (Payer et al., 2011).

During affect labelling, a measure of intrinsic emotion regulation, MAP participants showed comparable amygdala activity accompanied by a hypoactivation of the right VLPFC relative to healthy controls. Further decreased activation was found in the superior frontal gyrus, rolandic operculum and posterior cingulate cortex. These findings suggest a reduced cognitive engagement during emotion labelling, as was supported by the impaired task performance. The MA group, in contrast, displayed a significant overengagement of the left VLPFC, which may potentially indicate a compensatory activation to meet task-related cognitive demands to sufficiently regulate affect, or alternatively, may suggest a cognitive bias towards the negative facial emotions when engaging with the stimuli and verbally encoding the emotion.

Notably, whole-brain group comparisons demonstrated that both MA-dependent groups had to exploit more processing resources in visual occipitotemporal cortices during affect labelling than healthy controls. In MAP I found increased activity in the lingual and parahippocampal gyrus; both structures that have previously been implicated in emotional face processing in psychotic disorders (Li et al., 2009; Seiferth et al., 2008). In the MA group, increased activity was found in the calcarine sulcus, and inferior and middle temporal gyrus. Neural activation by emotional stimuli in visual pathways, including striate and temporal cortices has been shown to be influenced by the amygdala (Vuilleumier et al., 2004). Therefore, increased visual representations in response to the fearful and angry stimuli, with further modulation of extrastriate visual processing by the left VLPFC overactivation, may reflect a biased processing of the negative task stimuli in MA. Additionally, the MRI study of this thesis found structural changes in the pars triangularis to be associated with higher scores on the emotional reactivity scale in the MA group, suggesting VLPFC involvement in MA-related aberrant emotional behaviour. However, these inferences are rather speculative and further work investigating the mediating effects of the amygdala on sensory as well as socio-emotional processing networks in MA addiction is needed.

In the presented studies, I further investigated the association of MA-related changes in brain structure and function with psychotic symptoms in the MAP group, and found that reduced white matter integrity in posterior parts of the corpus callosum, the right posterior corona radiata and in the precuneus area was related to negative psychotic symptoms. The precuneus is implicated in self-attribution processes, reflective emotion processing, mental state attribution, and may be involved in guide attention to salient emotional or social stimuli (Cabanis et al., 2013; Lou et al., 2004). This suggests that structural disruption in this region may result in the mental disengagement associated with negative symptoms, including blunted affect and reduced motivation and interest, and may further underlie the observed social cognition dysfunctions in MAP.

Psychotic symptoms have also been shown to have an influential role on cortical activity during affect labelling relative to gender labelling in the MAP group.

Negative symptoms were associated with increased activity in the inferior and middle frontal gyrus, and anterior cingulate cortex, possibly reflecting a higher attentional and cognitive demand on patients with negative symptoms during intrinsic affect regulation. Positive symptoms, however, showed an association with increased activity in auditory cortices, insula and cuneus; structures that have previously been implicated in the experience of hallucinations.

Limitations

There were several limitations to the four research studies presented in this thesis. For example, one difficulty lied in the neuroleptic treatment in the MAP group, and its potential effects on the results of the studies have been thoroughly discussed in the corresponding chapters. Nevertheless, some of the main confounding factors are summarised here.

One major confound in this project is the use of drugs other than MA. Although participants with other drug dependencies (except for nicotine – which was necessary to facilitate recruitment) were excluded from this project, additive or interactive effects of tobacco smoking, cannabis and methaqualone use could not be disentangled from those of MA. However, across both MA-dependent groups, participants did not differ in any drug use measure, with the exception of study 3.

In addition, most studies involving illicit drug users rely on self-report of various drug use parameters. This is further complicated by the fact that, in South Africa, MA is sold in straws of different lengths and not in grams. Therefore, representative measures of MA quantities could not be reconstructed and possible dose-dependent effects could not be considered in this research.

Further, the use of self-report questionnaires can represent a confounding factor as the responder’s answers might not be reliable at all times. Therefore, future studies should incorporate a combination of objective behavioural tasks and self-report measures of affect regulation, to better characterise the study groups’ impairment in emotional behaviour.

As the recruitment of homogenous and perfectly matched study groups often presents a major challenge in research, it is recommended that future studies use larger sample sizes. Although this can be difficult with clinical populations and turn into a fairly time consuming process, it may, for example, allow for sub-group analyses of short-term versus long-term abstinence or of gender effects.

Last, all studies presented in this thesis were cross-sectional; hence a causal statement regarding the relationship between MA dependence and affect dysregulation cannot be made, nor can the causality of the structural and functional changes observed in the brains of MA-dependent individuals with and without a history of psychosis be ascertained. Longitudinal studies are needed to address this issue of causality as well as the issue of progressing brain changes as addiction and related psychopathology advance. Further, longitudinal assessment of the course of brain changes during abstinence from MA may help to disentangle brain alterations due to MA from effects attributed to other factors.

Conclusion

Despite these limitations, this thesis makes a substantial contribution to the existing literature, presenting novel findings on grey and white matter structural deficits and their association with affect dysregulation in MA dependence and MAP, in addition to new insights on aberrant cortical functionality during incidental affect regulation in these populations.

In conclusion, the studies clearly indicated significant difficulties in emotion regulation in individuals with MA dependence and MAP, as evidenced by high levels of aggression, emotional reactivity and impulsivity; with comparable deficits between the two groups. Further, both groups showed compromised abilities to identify social cues, indicated by reduced capacities in recognising facial emotions and inferring mental states; with significantly greater performance decrements in the MAP group. Such social cognition abilities are crucial to successful interpersonal functioning, and failure to recognise when aggressive behaviour is inappropriate may have destructive consequences on emotional and social behaviour. In MAP patients, behavioural impairments were underpinned by structural deficits in prefrontal and temporal brain region, evidenced by cortical thinning and reduced white matter integrity. Such association of grey and white matter pathology with difficulties in emotion regulation could not be shown to the same extent in the MA group, potentially suggesting subthreshold effects. However, aberrant neural functioning, established as frontolimbic hypoactivity during emotional processing in MAP patients and frontal hyperactivity during affect labelling in MA participants, may underlie the emotional behavioural problems seen in both groups.

Since emotional and social-cognitive impairments as well as psychotic symptomatology have been identified as contributing factors not only to negative social outcomes, but also to high relapse rates in MA addiction (Rawson et al., 2002), it may be useful for interventions to incorporate emotion-focused treatment, integrating aspects of socio-emotional perception and emotion regulation and aimed at enhancing such skills.

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Appendices

Part. ID					**Date**	DD	MM	YYYY

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**
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**

Part. ID					**Date**	DD	MM	YYYY

DERS

Please indicate how often the following statements apply to you by writing the appropriate number from the scale below on the line beside each item:

1	2	3	4	5
almost never	sometimes	about half the time	most of the time	almost always
(0-10%)	(11-35%)	(36-65%)	(66-90%)	(91-100%)

______ 1) I am clear about my feelings.

______ 2) I pay attention to how I feel.

______ 3) I experience my emotions as overwhelming and out of control.

______ 4) I have no idea how I am feeling.

______ 5) I have difficulty making sense out of my feelings.

______ 6) I am attentive to my feelings.

______ 7) I know exactly how I am feeling.

______ 8) I care about what I am feeling.

______ 9) I am confused about how I feel.

______ 10) When I'm upset, I acknowledge my emotions.

______ 11) When I'm upset, I become angry with myself for feeling that way.

______ 12) When I'm upset, I become embarrassed for feeling that way.

______ 13) When I'm upset, I have difficulty getting work done.

______ 14) When I'm upset, I become out of control.

______ 15) When I'm upset, I believe that I will remain that way for a long time.

______ 16) When I'm upset, I believe that I'll end up feeling very depressed.

______ 17) When I'm upset, I believe that my feelings are valid and important.

______ 18) When I'm upset, I have difficulty focusing on other things.

______ 19) When I'm upset, I feel out of control.

______ 20) When I'm upset, I can still get things done.

______ 21) When I’m upset, I feel ashamed with myself for feeling that way.

______ 22) When I’m upset, I know that I can find a way to eventually feel better.

______ 23) When I’m upset, I feel like I am weak.

______ 24) When I’m upset, I feel like I can remain in control of my behaviors.

______ 25) When I’m upset, I feel guilty for feeling that way.

______ 26) When I’m upset, I have difficulty concentrating.

______ 27) When I’m upset, I have difficulty controlling my behaviors.

______ 28) When I’m upset, I believe that there is nothing I can do to make myself feel better.

______ 29) When I’m upset, I become irritated with myself for feeling that way.

______ 30) When I’m upset, I start to feel very bad about myself.

______ 31) When I’m upset, I believe that wallowing in it is all I can do.

______ 32) When I’m upset, I lose control over my behaviors.

______ 33) When I’m upset, I have difficulty thinking about anything else.

______ 34) When I’m upset, I take time to figure out what I’m really feeling.

______ 35) When I’m upset, it takes me a long time to feel better.

______ 36) When I’m upset, my emotions feel overwhelming.

Part. ID					**Date**	DD	MM	YYYY

ERS

This questionnaire asks different questions about how you experience emotions **on a regular basis (for example, each day)**. When you are asked about being "emotional," this may refer to being angry, sad, excited, or some other emotion. Please rate the following statements.

0 Not at all like me	**1** A little like me	**2** Somewhat like me	**3** A lot like me	**4** Completely like me

1	When something happens that upsets me, it's all I can think about it for a long time.	**0**	**1**	**2**	**3**	**4**
2	My feelings get hurt easily.	**0**	**1**	**2**	**3**	**4**
3	When I experience emotions, I feel them very strongly/intensely.	**0**	**1**	**2**	**3**	**4**
4	When I'm emotionally upset, my whole body gets physically upset as well.	**0**	**1**	**2**	**3**	**4**
5	I tend to get very emotional very easily.	**0**	**1**	**2**	**3**	**4**
6	I experience emotions very strongly.	**0**	**1**	**2**	**3**	**4**
7	I often feel extremely anxious.	**0**	**1**	**2**	**3**	**4**
8	When I feel emotional, it's hard for me to imagine feeling any other way.	**0**	**1**	**2**	**3**	**4**
9	Even the littlest things make me emotional.	**0**	**1**	**2**	**3**	**4**
10	If I have a disagreement with someone, it takes a long time for me to get over it.	**0**	**1**	**2**	**3**	**4**
11	When I am angry/upset, it takes me much longer than most people to calm down.	**0**	**1**	**2**	**3**	**4**
12	I get angry at people very easily.	**0**	**1**	**2**	**3**	**4**
13	I am often bothered by things that other people don't react to.	**0**	**1**	**2**	**3**	**4**
14	I am easily agitated.	**0**	**1**	**2**	**3**	**4**
15	My emotions go from neutral to extreme in an instant.	**0**	**1**	**2**	**3**	**4**
16	When something bad happens, my mood changes very quickly. People tell me I have a very short fuse.	**0**	**1**	**2**	**3**	**4**
17	People tell me that my emotions are often too intense for the situation.	**0**	**1**	**2**	**3**	**4**

18	I am a very sensitive person.	**0**	**1**	**2**	**3**	**4**
19	My moods are very strong and powerful.	**0**	**1**	**2**	**3**	**4**
20	I often get so upset it’s hard for me to think straight.	**0**	**1**	**2**	**3**	**4**
21	Other people tell me I'm overreacting.	**0**	**1**	**2**	**3**	**4**

Part. ID					**Date**	DD	MM	YYYY

UPPS-P

Below are a number of statements that describe ways in which people act and think. For each statement, please indicate how much you agree or disagree with the statement. If you **Agree Strongly** circle **1**, if you **Agree Somewhat** circle **2**, if you **Disagree somewhat** circle **3**, and if you **Disagree Strongly** circle **4**. Be sure to indicate your agreement or disagreement for every statement below. Also, there are questions on the following pages.

	Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
1. I have a reserved and cautious attitude toward life.	1	2	3	4
2. I have trouble controlling my impulses.	1	2	3	4
3. I generally seek new and exciting experiences and sensations.	1	2	3	4
4. I generally like to see things through to the end.	1	2	3	4
5. When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.	1	2	3	4
6. My thinking is usually careful and purposeful.	1	2	3	4
7. I have trouble resisting my cravings (for food, cigarettes, etc.).	1	2	3	4
8. I'll try anything once.	1	2	3	4
9. I tend to give up easily.	1	2	3	4
10. When I am in great mood, I tend to get into situations that could cause me problems.	1	2	3	4
11. I am not one of those people who blurt out things without thinking.	1	2	3	4
12. I often get involved in things I later wish I could get out of.	1	2	3	4
13. I like sports and games in which you have to choose your next move very quickly.	1	2	3	4
14. Unfinished tasks really bother me.	1	2	3	4
15. When I am very happy, I tend to do things that may cause problems in my life.	1	2	3	4
16. I like to stop and think things over before I do them.	1	2	3	4
17. When I feel bad, I will often do things I later regret in order to make myself feel better now.	1	2	3	4
18. I would enjoy water skiing.	1	2	3	4
19. Once I get going on something I hate to stop.	1	2	3	4
20. I tend to lose control when I am in a great mood.	1	2	3	4
21. I don't like to start a project until I know exactly how to proceed.	1	2	3	4

	Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
22. Sometimes when I feel bad, I can’t seem to stop what I am doing even though it is making me feel worse.	1	2	3	4
23. I quite enjoy taking risks.	1	2	3	4
24. I concentrate easily.	1	2	3	4
25. When I am really ecstatic, I tend to get out of control.	1	2	3	4
26. I would enjoy parachute jumping.	1	2	3	4
27. I finish what I start.	1	2	3	4
28. I tend to value and follow a rational, "sensible" approach to things.	1	2	3	4
29. When I am upset I often act without thinking.	1	2	3	4
30. Others would say I make bad choices when I am extremely happy about something.	1	2	3	4
31. I welcome new and exciting experiences and sensations, even if they are a little frightening and unconventional.	1	2	3	4
32. I am able to pace myself so as to get things done on time.	1	2	3	4
33. I usually make up my mind through careful reasoning.	1	2	3	4
34. When I feel rejected, I will often say things that I later regret.	1	2	3	4
35. Others are shocked or worried about the things I do when I am feeling very excited.	1	2	3	4
36. I would like to learn to fly an airplane.	1	2	3	4
37. I am a person who always gets the job done.	1	2	3	4
38. I am a cautious person.	1	2	3	4
39. It is hard for me to resist acting on my feelings.	1	2	3	4
40. When I get really happy about something, I tend to do things that can have bad consequences.	1	2	3	4
41. I sometimes like doing things that are a bit frightening.	1	2	3	4
42. I almost always finish projects that I start.	1	2	3	4
43. Before I get into a new situation I like to find out what to expect from it.	1	2	3	4
44. I often make matters worse because I act without thinking when I am upset.	1	2	3	4
45. When overjoyed, I feel like I can’t stop myself from going overboard.	1	2	3	4

	Agree Strongly	Agree Some	Disagree Some	Disagree Strongly
46. I would enjoy the sensation of skiing very fast down a high mountain slope.	1	2	3	4
47. Sometimes there are so many little things to be done that I just ignore them all.	1	2	3	4
48. I usually think carefully before doing anything.	1	2	3	4
49. When I am really excited, I tend not to think of the consequences of my actions.	1	2	3	4
50. In the heat of an argument, I will often say things that I later regret.	1	2	3	4
51. I would like to go scuba diving.	1	2	3	4
52. I tend to act without thinking when I am really excited.	1	2	3	4
53. I always keep my feelings under control.	1	2	3	4
54. When I am really happy, I often find myself in situations that I normally wouldn't be comfortable with.	1	2	3	4
55. Before making up my mind, I consider all the advantages and disadvantages.	1	2	3	4
56. I would enjoy fast driving.	1	2	3	4
57. When I am very happy, I feel like it is ok to give in to cravings or overindulge.	1	2	3	4
58. Sometimes I do impulsive things that I later regret.	1	2	3	4
59. I am surprised at the things I do while in a great mood.	1	2	3	4

PARTICIPANT INFORMATION LEAFLET
AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:
Neural correlates of deficits in affect regulation in methamphetamine dependence with and without a history of psychosis

HREC REFERENCE NUMBER: 340/2009

PRINCIPAL INVESTIGATOR: Dr Donald Wilson

ADDRESS: University of Cape Town, Dept of Psychiatry and Mental Health, Groote Schuur Hospital (J2), Anzio Road, Observatory 7925, Cape Town, South Africa

CONTACT: E-mail:d.wilson@uct.ac.za, Phone: +27-21-404-2182, Fax: +27-21-448-8158

Dear Volunteer

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

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

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

What is this research study all about?

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

Methods: Participants will have to complete questionnaires and a series of behavioural 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 (Affect 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 (CUBIC, 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 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 50ml (10 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, DTI and MRS examination are performed in a special room that houses the MR system or "scanner". You will be escorted into the room by a staff member of the MRI facility and asked to lie down on a comfortably padded table that gently glides you into the scanner. This is typically a large, tunnel magnet that is open at both ends, so you won't be completely enclosed at any time.

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

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

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

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

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

Why have you been invited to participate?

Three groups of participants will be included in this study: methamphetamine (MA) abusers with a history of psychosis, MA abusers without a history of psychosis and non-substance-abusing healthy control subjects. Each of the groups will consist of 20 participants. You may fit into one of these categories as assessed during your initial screening.

What will your responsibilities be?

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

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

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

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

Will you benefit from taking part in this research?

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

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

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

Who will have access to your medical records?

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

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

If you withdraw your consent to participate in this study no new information will be collected from you and added to existing data or to a database. Your information will be processed electronically (i.e. by a computer) or manually and analysed to determine the outcome of this study. Your information may/could be sent to regulatory authorities and to the Ethics Committees. You have the right to ask the study doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any necessary corrections made to it.

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

If you become ill or injured as a direct result of your participation in this clinical study, you will be referred for appropriate medical treatment. The University of Cape Town’s insurance policy will cover the costs of such treatment. If you have any questions concerning the availability of compensation/medical care or if you think you have experienced a research-related illness or injury, contact details are below.

Your legal right to claim compensation for injury where you can prove negligence is not affected.

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

If you have questions about this study you should first discuss them with your study doctor or the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC), UCT.
Dr D. Wilson: (021)4042182
Dr H. Temmingh: (021)4403185
After you have consulted your doctor or the FHS HREC and if they have not provided you with answers to your satisfaction, you should write to the South African Medical Research Council at: Head Office Cape Town, Corporate Communications Office, Sarah Bok, PO Box 19070, Tygerberg, 7505, South Africa or Fax: (021)9380200.

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

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

Is there anything else that you should know or do?

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

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 .

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Signature of investigator