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TREATING HORROR WITH ECSTASY:
Neurobiological Rationale for Treating Post-Traumatic Stress Disorder with 3,4-methylenedioxymethylamphetamine

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Treating Horror with Ecstasy: Neurobiological Rationale for Treating Post-Traumatic Stress Disorder with 3,4-methylenedioxymethylamphetamine
Submitted by Anna Agelii to the University of Skövde as a final year project towards the degree of B.Sc. in the School of Humanities and Informatics. The project has been supervised by Oskar MacGregor.

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

Signature: _____

Abstract

Post-traumatic stress disorder (PTSD) is a disabling condition that afflicts 1-10% of the general population, with twice as high lifetime prevalence for women than men. Treatments exist, but none have proven reliable and consistent efficacy. A large minority of patients remain treatment-resistant despite undergoing several different types of treatment over extended periods of time. Recently completed studies in the U.S. and in Switzerland have demonstrated the potential of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treatment-resistant PTSD. One of the major problems of treating PTSD is the patients' fear state and inability to form a therapeutic alliance. Both these issues can be facilitated through administration of MDMA; the psychological effects - such as heightened empathy, increased openness and diminished anxiety – seem well-suited for therapeutic purposes. The rationale behind treating PTSD with MDMA has been indicated in neuroimaging studies; MDMA affects some of the neural structures altered in patients with PTSD, most notably the amygdala and the ventromedial prefrontal cortex. Using the Schedule 1 substance MDMA for this purpose is however controversial; animal studies have indicated that MDMA is neurotoxic, although no adverse effects on humans related to incidental use of MDMA in a controlled setting have been found. In conclusion, the data support that MDMA may be an efficient tool for treating PTSD, as well as safe and effective to use in a clinical context.

Keywords: Post-traumatic Stress Disorder (PTSD), 3,4-methylenedioxymethamphetamine (MDMA), ecstasy, psychotherapy, neurobiology

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Disorder with 3,4-methylenedioxymethylamphetamine

Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder that afflicts people

surviving traumatic incidents, especially if these were of human origin. It is relatively

common in the general population (1% in European countries), with higher prevalence in

countries engaged in armoured conflicts (8% in the U.S., estimates are higher for populations

in war zones) (Keane, Marshall, & Taft, 2006). About 20% of victims of violent crimes

develop PTSD (Charuvastra & Cloitre, 2008). War veterans, refugees, rape victims and

survivors of child abuse are most commonly diagnosed with this disorder. For example, 8

years after the genocide in Rwanda, almost 25% of the population suffered from PTSD

(Keane et al., 2006). Few effective treatments currently exist, and psychiatric co-morbidity is

high, as well as suicide rates. As the number of war veterans returning from battle and

refugees from conflict zones rises, finding a safe and effective treatment for this disorder

becomes critical (Keane et al., 2006). The aim of this essay is to investigate the

neurobiological rationale of treating PTSD with 3,4-methylenedioxymethamphetamine

(MDMA)-assisted psychotherapy.

The most common pharmacological treatment for PTSD is antidepressant drugs

(Steckler & Risbrough, 2012). Most of these drugs target the serotonergic system. The most

common are selective serotonin re-uptake inhibitors (SSRIs), which work by blocking the re-

uptake transporters in order to make more serotonin available in the synaptic cleft (Artigas,

2013; Nutt et al., 1999). Serotonin, or 5-hydroxytryptamine (5-HT) is a neurotransmitter

considered to be regulating mood, appetite, and sleep. Serotonin also helps regulate a number

of hormones, for example insulin and growth factors (Artigas, 2013; Nutt et al., 1999).

MDMA is a ring-substituted amphetamine derivative, belonging to the phenethylamines and amphetamines. Molecularly it also shares some characteristics with mescaline. Unlike other amphetamines, it is not primarily considered a stimulant, and neither as a hallucinogen like mescaline; but rather forms another group of psychoactive substances, together with its close relatives 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxy-N-ethylamphetamine (MDE): the *entactogens* or sometimes *empathogens* (Scahill & Anderson, 2010). Its unique psychological effects made it a popular tool for psychotherapy up until it was regulated in 1985, due to the increasing interest from recreational users. Since then it has mainly been known as the drug of choice for the rave scene, where it has been used illicitly under the name *Ecstasy* (Morton, 2005).

Recently completed clinical studies indicate that MDMA is effective in treating PTSD (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011, Mithoefer et al., 2012; Oehen, Traber, Widmer, & Schnyder, 2012).). Johansen and Krebs (2009) suggest a few mechanisms that could explain why MDMA is effective in treating anxiety disorders such as PTSD: its effect on oxytocin, on regulating activity in the ventromedial prefrontal cortex (vmPFC) and in the amygdala, and its effects on the release of norepinephrine and cortisol (Johansen & Krebs, 2009). In this essay I will investigate the empirical support for these claims, as well as MDMA's effect on the serotonergic system, which also seems to contribute to its therapeutic effects.

In order to do this the neural correlates of PTSD and MDMA are discussed in detail, as they are presently understood. But first there is an overview of PTSD and MDMA, followed by a presentation and evaluation of the contemporary studies of MDMA-assisted psychotherapy for treating PTSD. Issues concerning its neurotoxicity and potentially harmful psychological effects are discussed in the final section.

Recreational use of MDMA will not be covered, and therefore neither issues

associated with illicit use such as overdose or chronic heavy use nor effects resulting from

impurity. When using the term MDMA it refers to pure 3,4-

methylenedioxymethamphetamine, with equal ratio of both enantiomers[1]. Many studies on

the effects of MDMA does not discern between pure MDMA and Ecstasy, which probably

but not reliably contain MDMA. Some studies on recreational Ecstasy users are discussed,

but then clearly indicated that this is so by using the term Ecstasy, and not MDMA, even if

the original authors did not make that distinction. Thus whenever the term Ecstasy is used in

this essay it refers to the street drug that may or may not contain MDMA.

In this essay data from studies on brain activity, neurotransmitters, and hormones

pertaining to PTSD and MDMA are evaluated. The conclusion presented is that there is a

neurobiological rationale for treating PTSD with MDMA-assisted psychotherapy. It appears

to be safe to use in a controlled, clinical setting, and the efficacy of doing so shows

significant potential for remedying a previously treatment-resistant patient group.

PTSD

In this section an overview of the symptomatology and epidemiology of PTSD is

presented. The major symptoms of PTSD are re-experiencing symptoms (flashbacks,

intrusive thoughts, and images), emotional numbing, avoidance behaviour, and hyperarousal.

In neuropsychological terms this can be explained as deficits in extinction learning,

alterations in fear conditioning, and sensitization (Pitman et al., 2012). Sufferers of PTSD

demonstrate heightened autonomic reactivity, increased startle, and larger skin conductance

responses in reaction to stimuli related to the trauma, in comparison with people who have

been exposed to trauma, but did not develop PTSD (Zoladz & Diamond, 2013). In order to be

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[1] Most organic molecules exist in two variants, which are mirror images; these
variants are called enantiomers. Because this is also true for the molecules in human bodies,
different enantiomers often have different effects, for MDMA, the +-version is more potent
(Nichols, 2001).

diagnosed with PTSD the person must experience these symptoms for at least a month, after a

certain event, which was threatening to one self, or after witnessing death, injury or threat to

another person. Reactions to that event must include horror, fear, and helplessness (Steckler

& Risbrough, 2012). Psychiatric co-morbidity, especially depression and suicidal thoughts

and behaviours are common among PTSD patients. As these symptoms indicate, PTSD is a

disabling disorder often rendering the sufferer incapable of sustaining employment or having

a reasonable quality of life. Not only the afflicted person suffers from the symptoms of PTSD,

but the disorder also affects partners and family, both in the form of marital- and family

relationship problems and sexual dysfunction. Aggressive behaviour towards family members

is also not uncommon (Cukor, Spitalnick, Difede, Rizzo & Rothbaum, 2009).

Epidemiological studies indicate that traumas of human origin more often give rise to

PTSD than other traumas, such as natural disasters, which after less than 10% develop PTSD

(Charuvastra & Cloitre, 2008). Surveys also find that PTSD is more than twice as prevalent

among women than men, and even when exposed to same type of trauma, women are twice

as likely to develop PTSD (Nemeroff et al., 2006). Nemeroff et al. (2006) mention several

reasons as to why this might be so: genetic factors, type of trauma exposure, and

psychosocial factors. For example, women are more likely to be victims of sexual abuse,

which is often linked to shame and guilt. Women also more often have negative responses to

their traumatic experiences from family and friends (Nemeroff et al., 2006). That women

would have genetic predispositions towards developing PTSD is however challenged in a

recent review article by Zoladz and Diamond (2013). They suggest that there are no inherent

biological reasons as to why women would be more susceptible to PTSD than women; rather

it is women's higher risk of being victims of violence, as well as methodological flaws in

surveys that give the impression that women are more likely to develop PTSD. They also

point out that studies from the Iraq war could not corroborate that women would be more

sensitive to combat stress than men (Zoladz & Diamond, 2013). Regardless of reasons, in

absolute numbers more women than men suffer from PTSD (Keane et al., 2006).

As previously mentioned, traumas of human intent cause PTSD more often than other

events. Rape and other sexual assaults have the highest probability of generating PTSD in the

victims; 65% of male and 46% of female rape victims develop PTSD. Other traumas likely to

cause PTSD include childhood physical abuse (49% for women, 22% for men), being

threatened with a weapon (33% for women), and combat exposure (39% for men). In total,

traumas of human intent are twice as likely as traumas of nonpersonal nature to cause PTSD

(Charuvastra & Cloitre, 2008).

Charuvastra and Cloitre (2008) also discuss important factors, regardless of sex,

determining whether a person will develop PTSD after trauma or not: the level of subjective

distress and the level of social support. The latter is not only crucial in developing PTSD, but

also in the process of recovery. Strong, positive social support negatively correlate with

PTSD, and inversely, lack of social support, or negative social support, correlate with

severity of PTSD symptoms (Charuvastra & Cloitre, 2008). Low social support after trauma

is associated with avoidance behaviour, emotional numbing and withdrawnness (Charuvastra

& Cloitre, 2008). Avoidance behaviour, meaning that the patient actively avoids anything

reminding of the trauma, is a major risk factor towards developing PTSD. Another is feelings

of incompetence; the idea that if someone else had the same experience they would be able to

handle it, as is self-blame and guilt. Patients who view their PTSD as a sign of weakness also

have more difficulties recovering from the disorder (Nemeroff et al., 2006).

PTSD can be characterized as a chronic fear state, which makes therapy difficult. The

patient with PTSD constantly monitors the environment for threats, including also regarding

the therapist with distrust. Having a trusting relationship with the therapist is essential for

successful therapy so that the patient feels safe enough to remain and confront their thoughts

and feelings. The relationship with the therapist is a form of social bond, and is thus also

affected by the dysfunctions associated with PTSD, but a successful therapeutic alliance can

also mean gaining the positive effects of social support for the patient, especially since PTSD

patients often lack other kinds of social support (Charuvastra & Cloitre, 2008).

Neural Correlates of PTSD

This section will provide an overview of the neural structures primarily affected by

PTSD. Neural models of PTSD are mainly based on two different assumptions about brain

functioning. There is the "traditional" *neurocircuitry model* of PTSD, which emphasizes

medial-temporal and medial prefrontal regions in the pathophysiology of PTSD, and then

there is the more recent *triple-network model of psychopathology* (Patel, Spreng, Shin, &

Girard, 2012). This latter model is based on the assumption that PTSD, as most other

psychiatric conditions, arises from dysfunctions in three core brain networks: the default

network, the frontoparietal central executive network, and the salience network. These three

networks deal with different types of processing, but interact dynamically in an active brain.

Self-referential thinking, such as autobiographical memory is associated with activity in the

default network, while the central executive network deals with attention and working

memory. The salience network is thought to deal with autonomic functions and emotions, but

also conflict monitoring and reward-processing. The co-dependent manner in which these

networks interact means that disturbances in one part of the network will affect the others as

well: This could explain diverse symptomology in disorders such as PTSD (Patel et al., 2012)

This view enables the inclusion of abnormal activation patterns in areas of the parietal cortex,

precuneus, anterior insula, and the dorsal anterior cingulate cortex (dACC). Abnormal

readings in these areas in PTSD patients were not explained with the traditional

neurocircuitry model (Patel et al., 2012).

Regardless of what model one adheres to, PTSD is thought to progressively modify several brain structures; not only through neurochemical alterations but also by changing both brain function and structure. It has however been speculated that inborn brain abnormalities predispose some people to developing PTSD after traumatic incidents (Hull, 2002). One such predisposition can be a reduced cortical capacity for inhibiting fear (Pitman et al., 2012). A meta-analysis of 79 neuroimaging studies of PTSD patients indicates that middle parts of the anterior cingulate cortex (ACC), the dACC, and bilateral amygdala are the areas with most increased activity in these patients. The dACC is thought to be involved in response selection, fear learning, fear expression, error detection, and pain perception. Functional abnormalities in the dACC correlated with severity of PTSD symptoms (Pitman et al., 2012). They also found increased metabolism in dACC in war veterans with PTSD, as well as in their twins without PTSD (Pitman et al., 2012). In contrast, the vmPFC and inferior frontal gyrus were the regions demonstrating the largest decrease in activation (Pitman et al., 2012).

Compared to controls, PTSD patients seem to have a deficient reward system. Whether this means that a malfunctioning reward system predisposes for PTSD, or if PTSD damages the reward system is not clear. In an fMRI study of reward paradigms, reward stimuli elicited less signal change in PTSD patients for areas associated with reward: nucleus accumbens (NAcc), cingulate gyrus, the insula, and the PFC (Charuvastra & Cloitre, 2008). As previously mentioned; social support and feelings of safety are important protective factors with high impact on the likelihood of developing PTSD after a traumatic event, and also influence the recovery process from PTSD. Imaging data suggest that in order to feel trust the connections between amygdala and prefrontal cortices need to be functioning (Charuvastra & Cloitre, 2008), and these connections seem to be impaired in PTSD patients. Many studies have reported increased activity in amygdala and decreased activity in medial prefrontal regions when patients with PTSD undergo symptom provocation, either by, for example,

combat sounds and images, or by personal recollections (e.g., Shin et al., 2004).

Some neuroimaging studies have also indicated that sufferers of PTSD have decreased activity in Broca's area when experiencing trauma-related memories (Rauch, Shin, & Phelps, 2006). This area is understood to enable semantic representations of personal experiences. Decreased activity in Broca's area would then be one explanation as to why patients with PTSD experience difficulties structurally describing and communicating their trauma. It should however be noted that reactivation, and thus reconsolidation, of memories does not require the patient to semantically communicate said memory (Hull, 2002). This statement is partially contradicted by Brewin (2001), who proposes that reconstructing the traumatic experience verbally during therapy is important. Brewin (2001) argues that because trauma memories are usually hard for the PTSD patient to verbalize and correctly place in the autobiographical narrative, the intrusive flashback type memories can dominate. If the patient is able to consolidate a conscious, verbal representation of the memory this can help the mPFC to inhibit the fear response from the amygdala (Brewin, 2001).

The most commonly replicated finding in neuroimaging studies of PTSD is reduced hippocampal volume (e.g., Nemeroff et al., 2006; Pitman et al., 2012). Hippocampus is involved in encoding and recognition of episodic memories. The reduced hippocampal volume may be what underlies the deficits in extinguishing fear responses in combination with learning and memory (Patel et al., 2012). Damage to the hippocampi appears to be bilateral, and decrease in volume seems to correlate with severity of PTSD-symptoms. A study of war veterans with PTSD and their combat-unexposed identical twins however reported that hippocampal volume was comparable between the twins, and lower for both twins compared to war veterans without PTSD; suggesting that small hippocampal volume may be a risk factor for developing PTSD (Milad et al., 2008). Other studies however indicate that trauma-exposure may reduce hippocampal volume regardless of whether the

subject develops PTSD or not – or that smaller hippocampal volume may mean a

predisposition to experiencing trauma (Pitman et al., 2012). Other twin studies have however

indicated that hippocampal volume seems dependent on both genetic and environmental

factors (Nemeroff et al., 2006). Studies on children with PTSD, and adults that only recently

developed PTSD, did not find smaller hippocampal volumes; suggesting that it takes time for

hippocampal volume to decrease (Nemeroff et al., 2006). PET-studies also indicate that

activity in the right hippocampus decreases during symptom provocation (Nemeroff et al.,

2006).

In one study women with histories of childhood abuse, with or without PTSD, were

studied with fMRI during verbal memory encoding tasks. Women without PTSD exhibited

increased blood flow to the hippocampi, but those with PTSD did not (Nemeroff et al., 2006).

In relation to exposure therapy this is interesting. Because hippocampus is involved in the

context aspect of memories, efficient top-down inhibition from hippocampus and mPFC of

the amygdala is restricted to same context as the extinction learning took place in. In other

contexts, or when nonconsciously processing stimuli, the fear response may return (Brewin,

2001). Extinction learning largely involves the mPFC; in animal studies it has been

demonstrated that stimulating mPFC reduces fear-induced behaviour like freezing. Humans

undergoing extinction training exhibit increased activity in mPFC, and even thickening of the

mPFC cortices (Myers & Davis, 2006).

Accepted Treatments for PTSD

Many different forms of treatment have been devised for PTSD, ranging from

pharmacological interventions and psychotherapy to newer techniques such as Virtual Reality

and ancient ones such as yoga, just to name a few (Cukor et al., 2009). The best treatment so

far is considered to be a form of Cognitive Behavioural Therapy (CBT) called *exposure*

therapy (Cukor et al., 2009). Exposure therapy aims to desensitize the heightened emotional arousal, and is the most common treatment for PTSD (Cukor et al., 2009; Pitman et al., 2012).

Extinction learning, the key concept in exposure therapy, is a process involving re-exposure to the trauma or anxiety triggers in safe context; thereby recreating the painful memory with altered emotional content, until the memory or trigger no longer elicits an anxious response (Myers & Davis, 2006). The idea is to re-experience the trauma in this safe environment until the memory is habituated enough for resolving the PTSD (Charuvastra & Cloitre, 2008). A difficulty for this method to work on PTSD is that extinction learning is thought to be deficient in PTSD-patients. Hence one aim of exposure therapy is to re-establish normal functioning of this system. Earlier theories of exposure therapy believed that the fear-conditioned response was unlearned and replaced by the altered reaction. Later theories however acknowledge that the original coupling (stimuli-fear) is still present, just weakened by the inhibitions of the new associations. These are however context-dependent; so if the fear is successfully abolished in one setting, for example the laboratory, the fear still has a strong risk of returning in other situations (McNally, 2007). In order for CBT to be effective in treating PTSD, the therapeutic alliance must be strong, and the patient must feel safe enough to bring forward memories of the trauma. Not only does the patient need to feel safe, but emotional engagement is also essential (Jaycox, Foa & Morral, 1998). Since emotional numbing is one of the major symptoms of PTSD, this can be hard to achieve. Even though CBT has been very successful in treating many anxiety disorders it only demonstrates modest success in treating PTSD (McNally, 2007). Exposure therapy interventions are effective in about one third of the patients, but also have high dropout rates (Cloitre, 2009).

Pharmacological interventions, besides acute administration of benzodiazepines (sedatives), have so far been restricted to treatment of symptoms with SSRIs - but in studies no clinical effect has been seen (Cukor et al., 2009). Furthermore there is an on-going debate

concerning if SSRI is more effective than placebo even in treating its original application, depression (e.g., Fournier et al., 2010; Kirsch et al., 2008). Even though SSRIs are considered safe, and do alleviate some symptoms in a portion of patients with PTSD; there are also undesired side effects (e.g., loss of sex drive, weight changes, gastrointestinal effects), as well as the problem of slow onset of action. Improvement in symptoms is usually not noticeable until at least 3 weeks after initiation of medication (Nutt et al., 1999; Steckler & Risbrough, 2012). This is especially problematic in treating PTSD because of the high suicide rate – for a suicidal patient 3 weeks might simply be too long. Another downside to medicating PTSD patients with SSRIs and benzodiazepines is that these pharmacological agents can interfere with the process of extinction learning (Johansen & Krebs, 2009).

It has also been suggested that in order for a patient to recover, therapy should not only target the traumatic memories, but also work to improve the interpersonal relationships of the patient. This approach has been implemented with promising results. Even focusing only on the interpersonal relationships, without fear habituation at all, reduced PTSD symptoms in most participants (Charuvastra & Cloitre, 2008).

The most problematic portion of the afflicted patients is however treatment-resistant. This group is largely made up war veterans, those suffering from childhood abuse, and patients with comorbid mental health problems (Cloitre, 2009). Stein, Ipser, and Seedat (2011) conducted a review of 35 short-term randomized controlled trials of pharmacotherapy for PTSD. They concluded that regardless of type of medication, over 40% remain treatment-resistant. Real numbers might even be higher, as the publication bias may exclude studies with negative outcome (Stein et al., 2011). It is this patient group that is the primary target of MDMA-assisted psychotherapy.

MDMA

History of MDMA

MDMA was invented in the late 1800's, but was not patented until 1914 in Germany by the chemical company E. Merck as an intermediate chemical in the synthesis of hydrastisin, an anti-bleeding drug (Holland, 2001a). MDMA was then forgotten until the early 1950s when the U.S. army researched it for its potential use in brainwashing (Holland, 2001a). Only animal experiments were conducted at this time (Holland, 2001a). In the 1970s it was rediscovered and synthesized by the chemist Shulgin. Shulgin and Nichols (1978) were also the first to publish the human psychopharmacology of MDMA (Greer & Tolbert, 1986). Shulgin introduced the drug to friends and co-workers, among them therapists. Encountering the substance in this way led some of them to begin working with the chemical for clinical purposes (Holland, 2001a). One of those therapists was Zeff, who had previously worked with psychedelic therapy using LSD in the 1950s and 1960s (Sessa, 2007). Zeff came out of retirement to work with this novelty that many therapists found to be a powerful tool for psychotherapy. Thousands of patients were supposedly treated with MDMA, but no double-blind, placebo-controlled studies on the therapeutic effects were conducted during this time. Therefore the evidence of its therapeutic potential from pre-regulation times is to be regarded as anecdotal (Holland, 2001a).

In the 1980s MDMA found its way to the general public, and its use for recreational purposes became widespread. In the US this meant that despite having been used as a therapeutic tool for over a decade, MDMA was emergency classified as a schedule 1 controlled substance in 1985 (Holland, 2001a). Schedule 1 means that the substance is considered as having a highly addictive potential and no medical applications. Therapists now had to abandon MDMA as it was banned (Sessa, 2007), even though many opposed this

classification (Holland, 2001b). In a hearing of May 22, 1986 Judge Francis Young

recommended classification into Schedule 3, which would enable physicians to prescribe

MDMA and research to continue (Young, "Opinion and recommended ruling", 1986). The

DEA overruled and placed it in Schedule 1 (Holland, 2001b). Following recommendations

from the United Nations and the World Health Organisation, MDMA was classified

throughout most of the world during the 1970 – 1990's. Notable exceptions are Switzerland,

which allows use of MDMA for research purposes or therapy after special permission

(Holland, 2001b); and Portugal, which decriminalized use and personal possession of all

psychoactive substances in 2000 (Moreira, Hughes, Costa Storti, & Zobel, 2011).

Research on MDMA in the subsequent years focused on animal studies. These

experiments mainly concluded that MDMA is neurotoxic, especially in high doses taken

frequently (Holland, 2001a). In Switzerland there was a brief period, 1988 – 1993, when

some therapists were allowed to continue using MDMA for therapeutic purposes. A follow-

up study concluded that the vast majority of patients reported positive experiences, and

improvement in their well-being and quality of life (Sessa, 2007), which is conclusive with

the anecdotal reports from pre-regulation therapeutic use.

In 1992 Grob was allowed by the FDA to conduct human studies of MDMA, on

experienced Ecstasy-users. Since then small studies on recreational Ecstasy-users have been

allowed in the U.S. Studies have also been conducted in Switzerland, which traditionally has

been slightly more open towards research on psychedelics. In 1999 the nonprofit organisation

Multi-Disciplinary Association For Psychedelic Studies (MAPS) held a conference in Israel

on MDMA (Holland, 2001a), and in 2000 the first controlled study of MDMA-assisted

psychotherapy for PTSD was initiated in Spain (Doblin, 2002). Until then no documented

studies on therapeutic effects of MDMA seem to have been conducted (Iversen, 2006).

Acute Effects

As with most psychoactive substances, *set* and *setting* greatly influence the experiences of the subject after ingesting MDMA. The term set refers to the subject's expectations, motivations, and intentions and the therapist's mental state; as well as preparations, intended goal of the session, and the techniques utilized. Setting refers to the immediate, concrete environment where in the session is conducted. As these factors have major impact on the experience and outcome of the therapy session, planning is essential; as well as the relative well-being of the subject. Influenced by Stanislav Grof's publications regarding LSD-assisted therapy, Greer has published guidelines for how to conduct MDMA-assisted therapy (Greer & Tolbert, 1998). These were later updated and refined by Mithoefer et al. (2013) into a manual for treating PTSD with MDMA.

Physiological effects. The physiological symptoms experienced after ingesting MDMA in a controlled setting are generally mild and tolerable (e.g., Grob, 1998; Mithoefer et al., 2011; Oehen et al., 2012; Vollenweider, Gamma, Liechti, & Huber, 1998). Most commonly reported are elevations in blood pressure, pulse rate, and pupillary dilation. The cardiovascular effects and temperature are routinely monitored in clinical settings. Subjects also sometimes report trismus (jaw tension, teeth clenching, or grinding), dry mouth, insomnia, fatigue, and suppression of appetite (Bravo, 2001). Other effects include ataxia (difficulties coordinating muscle movements), tremor (shaking or twitching), palpitations (irregularity in heartbeat), sweating, difficulties concentrating, tingling, and drowsiness (Bravo, 2001). Higher body temperature is sometimes reported, but seems to be environmentally dependent (Davison & Parrott, 1997). When testing humans in the laboratory, no significant temperature rise have been observed, the highest being 0.4°C; and only in males (Liechti, Gamma & Vollenweider, 2001). In clinical studies there has been no serious adverse effects following MDMA administration (e.g., Mithoefer et al., 2012; Oehen,

2012).

Psychological effects. Vollenweider et al. (1998) investigated the psychological and cardiovascular effects of MDMA on healthy, MDMA-naive volunteers; using a randomized, double blind, placebo-controlled design, with a dose of 1.7 mg/kg MDMA. Psychological measures were taken during the peak of the experience, vital signs were monitored throughout the session and in addition the subjects undertook a Stroop test. The major findings of this study were that MDMA produced a state of enhanced mood and well-being, moderate derealisation (an alteration in the experience of the external world, making it seem unreal), depersonalization (a feeling of watching oneself from the outside, having no control over actions), and thought disorder (disorganized thinking). No depressive reactions were found. Some of these MDMA-naive subjects experienced some anxiety when the first signs of effects were detected, related to fear of loss of control. Vollenweider et al. discuss that if MDMA is used outside of the controlled clinical setting, this fear of losing control can lead to anxiety. There were no significant changes in reaction time or error rate on the Stroop test, which the authors suggest to mean that MDMA does not produce attentional deficits (Vollenweider et al., 1998). Transient, moderate increases in systolic and diastolic blood pressure was however measured, but was not apparent to subjects, who did not report any unpleasant physiological symptoms. Authors of this study conclude that modest doses of MDMA, defined here as 0.25-1.7 mg/kg, should not cause any physiological complications, but induce enhanced mood with moderate derealisation phenomena. In regard to aftereffects, about one third of subjects reported motor restlessness and difficulties in concentration up to 24 hours after being administered MDMA. Some also reported lack of energy, fatigue, and brooding the following day (Vollenweider et al., 1998).

Subjective effects. Johansen & Krebs (2009) conclude in their review that when MDMA is administered in a therapeutic setting it facilitates acceptance of one's self, induces

an increase in openness and acceptance for others, and enables patients to process traumatic or other negatively salient memories without fear or avoidance behaviour. This claim seems reasonable considering the consistency in reports of the acute subjective effects of MDMA. Most studies list the same or very similar symptoms, the exact wording depending on what scale was used to measure symptoms. These symptoms include enhanced communication, increased feelings of intimacy, feelings of euphoria and loving, greater self-confidence or self-acceptance, lowered defences, and transcendent experiences (Greer & Tolbert, 1986). Others report that subjects experienced feelings of happiness or euphoria, exhilaration and energy, warmth and friendliness, calmness, and relaxation (Davison & Parrott, 2007). Frei et al. (2001) reported elevated extroversion, increased thoughtfulness-contemplativeness, increased well-being, emotional excitability, relaxation, and calmness. A majority of subjects also experienced expanded mental perspective, insight into personal problems, and improved self-examination (Greer & Tolbert, 1986).

Liester, Grob, Bravo, and Walsh (1992) investigated the phenomenology, as well as the longer-lasting psychological and behavioural effects, of MDMA when used by 20 volunteering psychiatrists. The authors reasoned that choosing psychiatrists as subjects in their study would be advantageous, since the subjects would not only be knowledgeable in medicine and therefore capable to evaluate the physiological effects; but also be trained to observe and analyse the subjective effects. Furthermore they were considered to be well-suited to appraise the therapeutic potential of MDMA. These 20 psychiatrists evaluated their experience, and the following effects were experienced by more than 50%: Altered time perception (90%), increased ability to interact with or be open with others (85%), decreased defensiveness (80%), decreased fear (65%), decreased sense of separation or alienation from others (60%), changes in visual perception (55%), increased awareness of emotions (50%), and decreased aggression (50%). Some subjects also reported a diminished desire to perform

tasks, diminished libido, and higher levels of restlessness (Liester et al., 1992).

Aftereffects

The subjective adverse effects mainly occur one to three days after MDMA has been

consumed (Scott, Hides, Allen, & Lubman, 2012). Most studies however refer to adverse

effects occurring after ingestion of Ecstasy in a recreational setting; and therefore these are

difficult to separate from effects of other drugs, as well as effects of sleep deprivation and

extensive dancing. Some of these effects also seem to depend on the sex of the subject (Allott

& Redman, 2007), although others failed to find any link between sex and aftereffects (Scott

et al., 2012).

Short-term. In laboratory studies about one third of healthy subjects list the same or

similar short-term (1-3 days after use) aftereffects (e.g., Liechti et al., 2001; Vollenweider et

al., 1998). These include fatigue, anxiety, depressed mood, and impaired concentration

(Parrott & Lasky, 1998). The rate is higher for recreational Ecstasy users than in controlled

studies, but not even then do all users experience the same aftereffects. A study by Scott et al.

(2012) investigated factors associated with risk of experiencing these symptoms, using 33

Ecstasy-using volunteers and 21 abstaining controls. Their findings indicate that quality of

sleep correlated with perceived mood, regardless of consumption of Ecstasy. Their

conclusion is that Ecstasy has little effect on subacute mood, and that the confounding factor

in earlier studies was sleep deprivation (Scott et al., 2012). Sleep disturbances are sometimes

mentioned when discussing aftereffects, for example, 40% of the psychiatrists in the study by

Liester et al., (1992) reported decreased sleep. Scott et al. (2012) also found that contrary to

their initial hypothesis, pre-existing risk factors for mood disturbances did not correlate with

negative mood the days after Ecstasy consumption; and neither did being female, which has

been considered a risk factor for negative aftereffects in a few other studies (e.g., Allott &

Redman, 2007).

Long-term. Long-term (>3 days) aftereffects generally seem to be positive (e.g., Greer & Tolbert, 1986; Liester et al., 1992; Mithoefer et al., 2012; Parrott, 2007); including residual feelings of heightened empathy and emotional sensitivity as well as persistent elevated mood, increased acceptance, and calmness. In the 1992 study of Liester et al., 50% reported improved social/interpersonal functioning. 46% had changes in religious/spiritual orientation or practice. 45% reported changes in values or life priorities (described as being more interested in quality of life, less interested in material things, increased focus on relationships, more focus on education and learning etc.) and 40% improved occupational functioning (Liester et al., 1992). Exactly what is meant by improvement of occupational functioning was not made clear, but it seems reasonable that improved insight into oneself and increased openness and acceptance of others would be beneficial for a psychiatrist. Liester et al. also report that 85% of the subjects would take MDMA again, but all subjects denied having any drive, compulsion, or craving to do so. 85% were also in support of further clinical research on MDMA (Liester et al., 1992).

Studies focusing on long-term after effects corroborate the findings on short-term after effects by Scott et al. (2012). For example, Fisk, Murphy, Montgomery, and Hadjiefthyvoulou (2010) found no correlation between Ecstasy use and depressive symptoms; instead they found that combining Ecstasy and alcohol generally led to more adverse symptoms reported, but concurrent use of other drugs showed no correlation with adverse aftereffects. Other studies indicate that psychological symptoms and executive dysfunction is not associated with ecstasy consumption, but rather with use of other drugs (alcohol, cannabis, inhalants, and opioids) (Medina & Shear, 2007).

In controlled studies, aftereffects seem to lean towards the positive side (e.g., Greer & Tolbert, 1986; Liester et al., 1992; Mithoefer et al., 2012; Parrott, 2007). In a study of 29

subjects whom were administrated MDMA in a clinical setting, 18 reported positive changes in mood or emotional states, lasting from hours to weeks after MDMA consumption. 14 reported more good feelings, 11 felt more relaxed, calm, detached, serene, and/or less anxious. 23 of the 29 subjects reported positive changes in attitude, lasting from a week to a follow-up 2 years later (Greer & Tolbert, 1986).

Does MDMA Heighten Empathy?

A simple definition of empathy is that it means the ability to share others' affective states. As discussed by Singer and Lamm (2009), in social neuroscience, the concept is a bit more problematic to define than that. For a comprehensive review of the concept empathy, see Singer and Lamm (2009) or Walter (2012). Pertaining to the effects of MDMA on empathy, the division often favoured by cognitive neuroscientists of empathy into affective and cognitive empathy may be useful. Cognitive empathy refers to the ability to understand others' feelings and intentions, while affective empathy refers to the ability to feel what others feel, albeit with a meta-knowledge that discerns it from emotional contagion (e.g., laughing because others are laughing) (Walter, 2012).

In some studies the acute effects that have motivated the naming of MDMA as an entactogen or empathogen are emphasized. These include, besides those already mentioned, heightened empathy and sensual awareness, increased alertness, talkativeness, diminished anxiety, lowering of inhibitions, and increase of energy (Bravo, 2001). Bedi, Hyman, and de Wit (2010) investigated the claim that MDMA heightens empathy in a four-session, double-blind, within-subject design. 21 volunteers with self-reported previous, but limited, Ecstasy use were administered either low dose MDMA (0.75 mg/kg), moderate dose MDMA (1.5 mg/kg), methamphetamine (20 mg) or placebo. The participants undertook a series of emotional recognition tests.

The results indicated that MDMA (1.5 mg/kg) heightens sociability and decrease accuracy in facial fear detection, which in itself might enhance social behaviour. The authors discuss that the pro-social effects may be responsible for the perceived heightened empathy, but that detection of subtler emotional cues may be impaired (Bedi et al., 2010). This impairment in detection of subtle emotional signals may be beneficial for the therapeutic settings, because PTSD patients are over-sensitive in detecting negative cues even in their therapist (Bedi et al., 2010). Major weaknesses of the study to be considered is that the material used to measure detection of emotions were still photographs, and that all participants had previous experiences with MDMA (Bedi et al., 2010). Scahill and Andersen (2010) discuss the results of Bedi et al. and suggest that MDMA heightens affective empathy but impairs cognitive empathy. These ambiguous results make a clear conclusion difficult. Empathy is a difficult concept to define, and even more problematic to reliably measure. It might be that MDMA does not heighten empathy per se, but contribute in several ways that may enhance empathic ability in many patients.

Contemporary Treatment of PTSD with MDMA

The description of the acute and subacute effects of MDMA in the previous section may give indications as to why PTSD was the first disorder chosen for MDMA-assisted psychotherapy trials. The first double-blind phase-two clinical study on MDMA-assisted psychotherapy for PTSD was initiated in Spain in 2000 (Doblin, 2002). 29 women with persistent PTSD were enrolled in this study, but because of media and political pressure the study was discontinued after treatment of 6 subjects. Thus the sample size was too small to generate significant findings, but no adverse psychological effects were noted and all 6 subjects reported increased well-being. The study was randomized to contain three experimental sessions, one with a low dose of MDMA, one with a higher dose and one

placebo condition (Bouso et al., 2008).

Session outline

Mithoefer et al. (2013) outlined a plan for conducting MDMA-assisted psychotherapy, which will be summarized in the following section. All participants were prepared in two sessions before receiving MDMA-assisted therapy. The MDMA-sessions took place in a group psychotherapy room at a clinic, with two therapists present during all sessions, one male and one female. During the experience subjects were encouraged to lie down comfortably with eyes closed and focusing inward, while listening to pre-selected music. The therapists remained with the subject for the entirety of the session, but discussions were only conducted as need arose. It is specified in the manual that the sessions be conducted in a nondirective approach. The subjects are supposed to steer the experience themselves, albeit with help from the therapists, an approach that so far has yielded results (Mithoefer et al., 2011; Oehen et al., 2012) In all MDMA-sessions conducted by Mithoefer et al., the participants' trauma emerged without the therapists bringing it up. Although sexual contact is of course strictly forbidden, and this is included in the consent form; supportive physical contact, for example hand holding, is encouraged if instigated by the subject. After the session the participant stayed the night at the clinic in the company of a preselected companion (e.g., spouse). Integrative therapy sessions were conducted the morning after the MDMA-session, 1 week after and 2 weeks after. During the first week after treatment all participants were contacted by phone each day. In total subjects received two or three MDMA-assisted and 12 sessions of (non-drug) psychotherapy, with extra (non-drug) sessions available to those in need. 2 months after completion of the second session a final integration therapy session was conducted (Mithoefer et al., 2013). This plan was followed in both Mithoefer et al.'s (2011) and Oehen et al.'s (2012) studies, which are described in the next

sections.

U.S.

The second study, also double-blind phase two, was conducted in the U.S. by Mithoefer et al. (2011). 20 subjects partook in the study, all with treatment-resistant PTSD and a score of at least 50 (moderate to severe symptoms) on the Clinician Administered PTSD Scale (CAPS). The average duration of PTSD was 19 years, during which all subjects had undergone multiple medication trials, with selective serotonin re-uptake inhibitors (SSRI) or serotonin-norepinephrine re-uptake inhibitors (SNRI), as well as at least 6 months of psychotherapy (Mithoefer et al., 2011).

Medical history, physical examinations, and tests for example for blood count and HIV, as well as electrocardiograms (ECG) were administered, and all participants submitted negative drug screens. Psychological and neurocognitive tests were performed after enrolment, four days after each session, and 2 months after the second experimental session. The groups did not differ significantly at any of these tests neither at baseline nor at the 2-month follow-up (Mithoefer et al., 2011).

The sessions followed the method outlined above, with two MDMA-assisted sessions 3-5 weeks apart, with weekly non-drug therapy sessions in between. Participants ingested 125 mg of MDMA or placebo (lactose) in a capsule taken orally. In most of the sessions a second supplemental dose of 62.5 mg MDMA was given 2-2.5 h after the first dose. No medical complications were reported and no serious adverse effects occurred (Mithoefer et al., 2011).

Mithoefer et al. (2011) defined clinical response as at least a 30% decrease from baseline CAPS. After Stage 1 83.3% (10/12) of the MDMA group and 25% (2/8) in the placebo group met criteria for clinical response; 10/12 in the MDMA group, and 2/8 in the placebo group, no longer met DSM-IV criteria for PTSD. After Stage 2 the clinical response

rate was 100%. All subjects of the MDMA group that were unable to work due to their severe

PTSD symptoms were able to return to work after completion of the study. Improvement was

not limited to PTSD-symptoms; the majority of participants also reported increased self-

awareness, improved relationships, enhanced spiritual life, increased involvement in the

community, and generally increased quality of life (Mithoefer et al., 2011).

Mithoefer et al. (2012) performed a long-term follow-up study 2-5 years (mean 3.5

years) after the original study. All 20 subjects from the original study participated in this

follow-up. Results from this follow-up study show no statistical differences in CAPS scores

between the 2-month follow-up and the 2-year follow-up. All participants reported benefits

from partaking in the study and no one felt they were harmed in any way by participating. At

enrolment, 84% of participants were undergoing psychotherapy; at the 2-year follow-up 42%

were in active psychotherapy. The rate of participants under psychiatric medication remained

the same, 58%, but mean number of medicines taken decreased from 1.7 to 1.3. No new illicit

substance use was reported, although rates of incidental cannabis use remained the same as at

the time of enrolment (Mithoefer et al., 2012).

Switzerland

A third study was recently conducted by Oehen et al. (2012) in Switzerland with 12

participants, using a randomized, double-blind, active-placebo controlled design. All

participants suffered from treatment-resistant PTSD, with a CAPS score of >50. Participants

in this trial either received a low-dose MDMA (25 mg + 12.5 supplemental dose), full-dose

MDMA (125 mg + 62.5 mg supplemental dose) or placebo (Oehen et al., 2012). The

rationale of using low-dose MDMA as an active placebo (an active placebo is a placebo that

has some effects of the target drug, often the side effects, but not the main effect) was to

minimize breach of the double-blind protocol, in order to ensure that participants remained

naive to what condition they were under. This strategy was successful in order to maintain blindness, but even though it is generally thought that a dose of 80 mg of MDMA is necessary for apparent subjective effects, 3 subjects in the active-placebo group experienced mild symptoms. These included spontaneous recall of traumatic memories accompanied by intensified negative emotions, but the low-dose MDMA did not induce the maximum fear reduction and positive integration of full-dose MDMA. These circumstances led to participants in the active-placebo group to require more support from the therapists during the session, as well as more psychotherapy sessions to integrate their experiences than the full-dose group (Oehen et al., 2012).

The study utilized a three-stage design, with participants receiving active placebo in the first stage being offered to open-label MDMA-treatment in stage 2. All active-placebo participants chose to continue into stage 2. Subjects who did not significantly improve after stage 2 could continue to stage 3, where a slightly higher dose (150 + 75 mg) was administered. Both CAPS and the Post-Traumatic Stress Diagnostic Scale (PDS) were used to measure outcome. In total, participants thus received three treatments with MDMA as well as non-drug psychotherapy (Oehen et al., 2012).

Follow-up assessments were conducted 3 weeks after the last treatment, 2 months later and 1 year later. No adverse effects were recorded. CAPS scores were not significantly reduced, although had continued to decrease at the 1-year follow-up. PDS scores on the other hand significantly improved. Three treatments with MDMA were statistically more efficient than two treatments. At the 1-year follow up one of the subjects had died of causes unrelated to the study, 5 of the 12 subjects no longer met the criteria for PTSD, 2 had mild PTSD, and 4 had moderate PTSD (Oehen et al., 2012).

Unfinished studies

MAPS (2013) report that several phase two studies are underway in different countries; most media coverage has the coming study in Canada received. Studies are also underway in Israel, Australia, and United Kingdom; and several trials are in different stages of execution in the United States. Mithoefer and his team are currently conducting a randomized study of military veterans with PTSD; this time using low, medium, and full dose MDMA, similar to the Switzerland study. There is also another study underway, which aims to administer open-label MDMA-assisted psychotherapy to those who have already undergone and responded well to prior sessions but relapsed after a year or more. MAPS and the FDA are currently collaborating to instigate phase three studies, which will involve hundreds of subjects in several countries (MAPS, 2013).

Neurobiological Rationale for Treating PTSD with MDMA

Johansen & Krebs (2009) suggest that the combination of MDMA's pharmacological effects both facilitates recall of traumatic memories, enhances emotional activation, and makes the patient feel safe and in control. This is purportedly accomplished through the increase in levels of norepinephrine, cortisol, and oxytocin that MDMA induces; and on the observed increased activity in vmPFC and decreased activity in amygdala (Johansen & Krebs, 2009). This assumption is in part corroborated by for example Oehen et al. (2012). They suggest that the effect on norepinephrine and cortisol levels may enhance extinction of learned fear associations, which may be one reason why it is effective in treating PTSD (Oehen et al., 2012). In the following sections the empirical data regarding neurotransmitters, regulation of activity, and hormones in conjunction with PTSD and MDMA will be discussed.

Neurotransmitters

Several different neurotransmitters have been implicated in the psychopathology of PTSD. Dysfunctions are found in the noradrenergic, serotonergic, and glutamatergic/GABAergic systems (McFarlane, Yehuda, & Clark, 2002; Pitman et al., 2012; Ravindran & Stein, 2009; Steckler & Risbrough, 2012). In theory, and in vitro, MDMA inhibits the vesicular monoamine transporters; which prevents re-uptake of serotonin, norepinephrine, and dopamine; and therefore increase levels of these neurotransmitters in the synaptic clefts. Unlike other amphetamines no significant release, and no subsequent depletion, have been found of norepinephrine or dopamine in vivo (Green, Mechan, Elliott, O'Shea, & Colado, 2003; Iversen, 2006).

The release of dopamine depends on the extent of 5-HT release, because activation of the 5-HT$_{2A}$-receptor increases synthesis and release of dopamine. The MDMA-propagated release of dopamine is dose-dependent and mainly occurs in the striatum and NAcc, similar to the effects of d-amphetamine and methamphetamine (Green et al., 2003). A clear difference can however be seen in elicited EEG patterns: Alpha activity is increased by d-amphetamine and methamphetamine, but decreased by MDMA (Frei et al., 2001). Pre-treatment with the dopaminergic D2 antagonist haloperidol reduces the euphoric effect of MDMA as well as increase negative effects (negative derealisation), but do not reduce cardiovascular effects (Vollenweider, Geyer & Greer, 2001). Even though dopamine is not generally implicated in PTSD, the indirect effects of MDMA on the dopaminergic system could be disadvantageous. There are indications that increases in dopamine levels disrupt extinction learning, especially retention of extinction. However, these claims come from animal studies, wherein cocaine was administered during extinction learning, thus it is possible that the detrimental effect on retention could be state related (Myers & Davis, 2006).

With regard to the glutamatergic/GABAergic system, PTSD is associated with

reductions in GABA receptor binding throughout the cortex, hippocampus, and thalamus

(Pitman et al., 2012). Glutamate is the main excitatory neurotransmitter, and γ-aminobutyric

acid (GABA) the main inhibitory neurotransmitter in the mammalian brain. They are

essential for extinction learning, both in expression and consolidation of the extinction

(Myers & Davis, 2006). Even though it has been demonstrated that MDMA increase

extracellular levels of GABA, it may also decrease levels in the substantia nigra (Bankson &

Yamamoto, 2004). Thus MDMA may affect the glutamatergic and GABAergic systems in a

way pertinent to PTSD, but this mechanism is less well studied and beyond the scope of this

essay to discuss further. Norepinephrine and serotonin will be discussed in more detail in the

following sections.

Norepinephrine. That PTSD would be coupled with deficits in the noradrenergic

system is perhaps not surprising, as norepinephrine is the primary agent in the stress response

of the sympathetic nervous system. A consistent find in PTSD patients is that the

noradrenergic system is hypersensitive, which means that norepinephrine is released in

response to relatively weak stimuli (Zoladz & Diamond, 2013). Elevated levels of

norepinephrine have been found in most studies of patients suffering from PTSD; but when

comparing trauma-exposed individuals with nonexposed individuals, trauma exposure,

regardless of developed PTSD or not, correlated with increased levels of norepinephrine

(Ravindran & Stein, 2009). Whether this means a predisposition to experiencing trauma or

that it is elicited by the trauma is not clear (Zoladz & Diamond, 2013). All subjects with

PTSD did however exhibit elevated levels of norepinephrine, whether measured in the CSF,

plasma, or urine (Ravindran & Stein, 2009).

Neurons producing norepinephrine are mostly located in an area of the brainstem called

locus ceruleus, which projects to the amygdala, hippocampus, PFC, and the thalamus

(McFarlane et al., 2002); areas where abnormal activity can be seen in PTSD patients.

Norepinephrine has been found to modulate amygdala activity, and elevated levels of

norepinephrine correlates with decreased activity in the PFC (Ravindran & Stein, 2009).

Norepinephrine is also involved in consolidation and retrieval of threatening memories

(Myers & Davis, 2006), mainly through amygdala's linkage to the hippocampus (Ravindran

& Stein, 2009).

Some evidence does point to norepinephrine playing a role in the effects of MDMA

though, such as EEG patterns during acute MDMA administration. These display similarities

with the EEGs obtained when the norepinephrine uptake inhibitors tandamine and

ciclopramine are administered (Frei et al., 2001). The main effect of MDMA on

norepinephrine is probably mediated through its major effects on serotonin (Liechti &

Vollenweider, 2001), which will be discussed in the following section.

Serotonin. As previously mentioned, MDMA works as a re-uptake-inhibitor on the

serotonergic system. In animals, including humans, serotonin is synthesized from the

precursor L-tryptophan, mediated by the enzymes tryptophan hydroxylase (TPH) and amino

acid decarboxylase. Serotonin is too large to enter through the blood-brain barrier (BBB), and

thus must be synthesized in the brain. The majority of the brains serotonin is synthesized in

the dorsal raphe nucleus. Its precursors, L-tryptophan and the metabolite 5-

hydroxytryptophan (5-HTP) can cross the BBB however. Serotonin is metabolized to 5-

hydroxyindoleacetic acid (5-HIAA), which can be measured in the urine or in the

cerebrospinal fluid (CSF) (Nutt et al., 1999).

MDMA increases levels of serotonin in the synaptic cleft by several mechanisms. By

occupying the 5-HT transporter and preventing 5-HT from binding to it, the amount of 5-HT

in the synaptic cleft increases. MDMA however not only blocks the transporter; it is small

enough to utilize the 5-HT transporter in order to be deposited into the presynaptic cell.

Inside the presynaptic serotonergic cell it induces further release of 5-HT into the synaptic

cleft. MDMA then again binds to the transporter, is released into the presynaptic cell, falls off and lets 5-HT bind to the transporter, to be released into the cleft where the transporter again can bind MDMA. Continuing the circle in this way the serotonergic cell is eventually depleted of all serotonin. Since MDMA blocks the re-uptake transporter the synaptic cleft is flooded with 5-HT, which eventually dissipates out from the cleft (Iversen, 2006).

Another mechanism that contributes to increased levels of 5-HT is the inhibition of MDMA on the enzyme complex monoaminooxidase A, which degrades 5-HT (Hasler, Studerus, Lindner, Ludewig & Vollenweider, 2009). Thus the degradation of serotonin slows down. MDMA also temporarily inactivates TPH, which is needed to synthesize more 5-HT from its precursors. This means that while cells are depleted of serotonin, no more can be produced until the effect on the enzyme wears off, which it does within 24 hours. However, if MDMA is administered repeatedly during this period, longer-lasting depletions of serotonin results (Malberg & Bonson, 2001).

In rodents administration of 5-HT_{1A} antagonists decreases the pro-social behaviour induced by MDMA, suggesting that binding to these receptors are central to the effects of MDMA (Morley, Arnold, & McGregor, 2005). It is however not certain that this find is translatable to human psychopharmacology. Hasler et al. (2009) investigated the role of the 5-HT_{1A}-receptor in human psychopharmacology of MDMA by using pre-treatment with the 5-HT_{1A}-blocker pindolol. They found that blocking the 5-HT_{1A}-receptor only slightly altered the subjective experiences and cognitive performance after ingesting MDMA, suggesting that these receptors may not be as important in the psychopharmacology of MDMA as previously thought. The relatively low dose of pindolol (20 mg) might however have been insufficient to block enough receptors (Hasler et al., 2009). This may however mean that the pro-social effects of MDMA, unlike in rodents, in humans do not involve the 5-HT_{1A} receptors like Thompson, Callaghan, Hunt, Cornish, and McGregor (2007) suggest.

Alterations in the serotonergic system have been indicated to cause deficits in learning and memory, for example in rats, where excessive 5-HT release leads to memory impairment (Santucci, Knott, & Haroutunian, 1996). Contrary to this, Hasler et al. (2009) found that MDMA induced facilitated memory recollection, but also diminished attention capacity when attention was supposed to be maintained over extended time periods (Hasler et al., 2009). Hasler et al. speculate that these are connected; increased ability to recollect memories may mean that subjects become easily distracted.

In animal studies MDMA administration has been followed by a reduction in serotonergic neurons, depletion of brain 5-HT and 5-HIAA, inhibition of TPH-activity, and alteration in density of 5-HT re-uptake sites (Curran, 2000; Parrot, 2001). Animal studies indicate that for long-term neurotoxic effects to appear either a very large dose (20 mg/kg) or large doses (5 mg/kg) twice daily for four consecutive days is required. These large doses are motivated by the interspecies scaling technique (Green et al., 2003), but it should be noted that conversion of doses between species is not straightforward, although there is controversy in the matter (Curran, 2000; Halpern, 2004; Jager et al., 2007; Kish, 2002; Lyvers & Hasking, 2004; Vollenweider et al., 2001). Long-term studies indicate that restoration of damaged areas may occur within a year of last administration (Iversen, 2006), the rate of recovery does however seem to vary between different species, and may be persistent in some (Curran, 2000). For example, nonhuman primates receiving 5 mg/kg twice daily for four days exhibit regional differences (increase in hypothalamus, decrease in neocortex) in recovery of 5-HT transporters 9 and 13 months after administration (Morgan, 2000).

The serotonergic system is less well studied in PTSD than the noradrenergic. A replicated find is that patients with PTSD have decreased 5-HT transporter binding in the amygdala (Pitman et al., 2012). Treatment with SSRI has been demonstrated to alleviate symptoms in some patients. Whether by decreasing co-morbid depressive symptoms or

actually treating the PTSD is not clear. SSRIs have however been indicated to increase

hippocampal volume, and since PTSD is coupled with decreased hippocampal volume, this

might be the source of the therapeutic benefit (Ravindran & Stein, 2009). Other studies have

indicated that SSRI administration (in healthy volunteers) decreases activation in the

amygdala during processing of emotional faces. Serotonin also inhibits release of

norepinephrine, thus an increase in available serotonin might help modulate the anxious state

induced by hypersensitivity of the noradrenergic system (Ravindran & Stein, 2009).

MDMA thus increases the amount of serotonin available in the synaptic clefts. This is

probably the major mechanism inducing the enhanced positive mood, even euphoria, in

patients administered MDMA (Gamma, Liechti, & Vollenweider, 2001). This provides the

immediate benefit of releasing the patient from the comorbid depression that is common in

PTSD patients. For a chronically depressed patient feeling good, even briefly, may provide

hope and strength to continue the recovery process (Riedlinger & Montagne, 2001). Increased

levels of serotonin may facilitate memory recall, which can benefit the therapeutic process

(Hasler et al., 2009). Increased serotonin also contributes to decreasing levels of

norepinephrine, which lowers anxiety and may increase activity in PFC (Ravindran & Stein,

2009). Increased activity in PFC may mean enhanced inhibition of fear responses from the

amygdala (Patel et al., 2012).

Regulation of Activity

MDMA modulate neuronal activity in cortical and subcortical areas considered to be

regulating mood and emotion (Vollenweider et al., 2001). Following administration,

increases in activity can be seen in vmPFC, ACC, inferior temporal lobe, medial occipital

cortex, and in the cerebellum. Conversely, MDMA decreases activity in the motor and

somatosensory cortices, the superior temporal lobe, the dorsal anterior and posterior cingulate

cortex, the insula, the thalamus, amygdala, right hippocampus, and the uncus (Vollenweider et al., 2001).

MDMA has been demonstrated to increase activation in the ventral striatum and the rate of detection of friendly faces and positive expressions, as well as decrease accuracy of facial fear recognition (Bedi, Phan, Angstadt, & de Wit, 2009, Bedi et al., 2010; Hysek, Domes, & Liechti, 2012). The ventral striatum is activated in association with feelings of well-being, reward anticipation, and happiness. Subjective reports of facilitated social communication and interaction correlated with activity in temporal cortex, amygdala and orbitofrontal cortex. These regions form the basolateral circuit, and are believed to mediate social communication (Vollenweider et al., 2001).

In an fMRI study on the effects of MDMA on sociability it was found that MDMA attenuates amygdala activation to angry faces, but not to fearful ones (Bedi et al., 2009). The same study found that MDMA increased activation in the ventral striatum when subjects were presented with happy faces. The interpretation was that MDMA dampens neural responses to threat-related social stimuli and increases responses to positive social signals. These effects were dose-dependent; low-dose MDMA (0.75 mg/kg) affected neural responses but not subjective ratings unlike normal-dose (1.5 mg/kg), which had impact on both neural responses and self-reported sociability (Bedi et al., 2009). Whether subjective experience of this effect is necessary for therapeutic efficacy is not clear, although some studies indicate that it is (Oehen et al., 2012).

Amygdala and the ventral medial prefrontal cortex. The amygdala is associated with fear response, fear recognition, fear expressions, and fear learning as well as emotional content of memories. Activation of the amygdala is thus associated with fear, threat responses, and detection of negative social signals (Shin et al., 2005). It is thought that when the brain responds to threatening stimuli, the fast route travels from visual cortex directly to amygdala,

which initiates a rapid stress response. The amygdala then initiates release of stress hormones (Brewin, 2001). PTSD has been associated with an over-active amygdala, which produces exaggerated reactions to stimuli connected with the trauma (Shin et al., 2005). Empirical data from neuroimaging studies support this theory; patients with PTSD consistently exhibit increased activity in the amygdala (Pitman et al., 2012).

The medial prefrontal cortex (mPFC) has been demonstrated in extensive animal research to suppress fear responses through its connections to the amygdala. As might be suspected, several areas of the mPFC exhibit hypoactivation in sufferers of PTSD, most notably the ACC and the vmPFC (Patel et al., 2012). The vmPFC has been demonstrated in animal studies to be damaged by chronic stress, and decreased volume of vmPFC is one of the most common findings in neuroimaging studies of PTSD patients (Hull, 2002).

Patel et al., (2012) emphasize that the connectivity of mPFC with other areas, especially amygdala, is important for the understanding of the neural correlates of PTSD. The top-down inhibition of the amygdala from the vmPFC is thought to be deficient in PTSD patients (e.g., Pitman et al., 2012; Shin et al., 2005). Diffusion tensor imaging studies of PTSD patients exhibit impaired white matter integrity in the cingulum bundle, a neuronal tract connecting the ACC and the amygdala. Impaired connections between these areas may be one reason for the deficit top-down control from the prefrontal cortex to the amygdala (Pitman et al., 2012).

This is corroborated by studies of patients with PTSD that have indicated that when the amygdala responds to stimuli associated with the trauma, activity in the prefrontal cortex decreases (Hull, 2002). Other studies on human subjects seem to confirm these conclusions. In a study by Shin et al. (2004), Vietnam War veterans, both male and female, with and without PTSD, were studied with PET while exposed to audiotapes composed of trauma-reminding material. They discovered an inverse relationship between activity in the mPFC

and the amygdala for participants suffering from PTSD. Severity of symptoms correlated with decrease of activity in mPFC and increase in activity in the amygdala (Shin et al., 2004).

This has been replicated in other studies that indicate that decreased activity in vmPFC is reliably negatively correlated with severity of symptoms and that improvement of PTSD symptoms correlate with increased activity in parts of the vmPFC (Pitman et al., 2012). Lower activity in amygdala has also been found to correlate with positive mood states (Vollenweider et al., 2001). The hyperactivation of the amygdala in combination with deficit inhibition from the vmPFC could explain the hyperarousal and vivid recollections ("flashbacks") of traumatic memories experienced by sufferers of PTSD (Patel et al., 2012). It has also been hypothesized that since the amygdala projects to all regions of the brain involved in visual processing, this could contribute to explaining the flashbacks (Brewin, 2001). Interestingly, the level of hyperactivation of amygdala in PTSD-patients also correlates with unsuccessful outcomes of cognitive behavioural therapy (Patel et al., 2012).

One fMRI study however indicated that PTSD patients may have increased activation of mPFC, instead of decreased activity, when nonconsciously processing fear stimuli (Bryant et al., 2008). The authors of this study also concluded that the heightened activity in amygdala is especially prominent when responding to rapidly presented stimuli. In healthy subjects mPFC exhibit increased activity during nonconscious processing of fear, activity that seems to originate in the brainstem travels through amygdala and into the mPFC in a feed-forward manner (Bryant et al., 2008). Differences in activation were especially notable in participants with PTSD compared to healthy controls; PTSD patients demonstrated larger increase in activity in the amygdala and mPFC (Bryant et al., 2008). This heightened activity of mPFC has not been seen in conscious processing however, implicating that the impairment of mPFC in PTSD patients is top-down only, while the rapid response to fear is increased. This might explain why PTSD patients are in a state of constant fear – the nonconscious

processing of fear is working over-time while the modulation from top-down connections is impaired (Bryant et al., 2008).

Shin et al. (2005) investigated whether the increased amygdala activity and decreased mPFC activity, previously demonstrated for PTSD patients when processing trauma-related stimuli, would also be present when consciously processing fearful but not trauma-related material. A particular strength of this study was that the control group consisted of trauma-exposed participants without PTSD. Results indicate that PTSD patients do indeed have increased amygdala and decreased mPFC activity compared to controls (Shin et al., 2005). In all these studies activity correlated with PTSD symptom severity, and activity in amygdala was negatively correlated with activity in mPFC (Bryant et al., 2008; Shin et al., 2004, 2005). Laterality seems to play a certain role; in some studies of PTSD patients the right amygdala exhibited larger increases in activity (Shin et al., 2004, 2005).

Increasing activity in the vmPFC, and therefore its inhibition of the amygdala-mediated fear response, reduces avoidance behaviour and fear; thereby facilitating the revisiting of painful or traumatic memories. This may enable the reconsolidation of the traumatic memories that is essential to extinction therapy (McNally, 2007). Studies on the neural correlates of extinction learning indicate that if the mPFC is damaged extinction learning no longer function normally (McNally, 2007). Amygdala is also involved in the extinction of fear responses: During all phases of extinction learning activity in the amygdala increase (Myers & Davis, 2006).

In addition to decreasing activity in the amygdala, MDMA has been found to increase activity in the vmPFC (e.g., Gamma, Buck, Berthold, Hell, & Vollenweider, 2000). Studies on both rats and humans indicate that increased activity in vmPFC during exposure to traumatic memories has therapeutic benefits. It seems like these modulations of activity would be remarkably well-suited to regulating the abnormal activity patterns of PTSD

patients.

Hormones

    Cortisol. PTSD does not seem to be accompanied by increases in cortisol levels – as one could assume because of the relationship between other types of chronic stress and cortisol. Cortisol administration has even been found beneficial for some PTSD patients, perhaps because of its inhibitory effect on memory retrieval (Pitman et al., 2012). Both administrations of cortisol and of norepinephrine before exposure therapy has been demonstrated to enhance extinction learning (Ravindran & Stein, 2009), but also to exaggerate anxiety in PTSD-patients, making the experience unbearable for the patient – and administering anti-anxiety drugs interfere with the extinction process (Johansen & Krebs, 2009). Other studies however imply ambiguous results – some indicate that PTSD patients have a low baseline of cortisol, but will release excessive amounts in response to stressful stimuli (Nemeroff et al., 2006). Since the amygdala propagate release of stress hormones, and PTSD patients have overactive amygdala, this seems plausible.

    MDMA ingestion has been demonstrated in several studies of recreational Ecstasy (albeit MDMA confirmed by urinary or saliva analysis) users to increase cortisol levels (e.g., Parrot, Lock, Adnum, & Thome, 2012; Wolff, 2005; Wolff & Aitchison, 2012) but in what degree is debated. Wolff (2005) suggests that the increase in cortisol levels is about 110%, while Parrott et al., (2012) proposes 800%. Wolff and Aitchison (2012) however replied that they measured plasma cortisol and Parrott et al. measured saliva concentrations. All measurements were however of people taking Ecstasy in dance clubs, and neither Parrott et al. nor Wolff and Aitchison mention if the participants refrained from other drugs during the study. Both these factors decrease the ecological validity. Other confounding factors seem to be the fact that cortisol levels depend on circadian rhythms and genetic variations (Wolff &

Aitchison, 2012).

If cortisol enhances extinction learning, the MDMA propagated release of cortisol may be beneficial for PTSD patients. The decreased anxiety and enhanced mood induced by MDMA may give the benefits of cortisol administration, while avoiding the excruciating anxiety that makes successful therapy impossible.

Oxytocin. The hormone oxytocin is produced in the hypothalamus (Marsh, Yu, Pine, & Blair, 2010) and has been demonstrated to increase prosocial behaviour (Charuvastra & Cloitre, 2008). It facilitates social bonding and was firstly known as the nursing hormone, as it is released in abundance during and after childbirth and while nursing. Later it has also been demonstrated to mediate social bonding in adults, especially in females. Arginine vasopressin serves some of these functions in males (Heinrichs, von Dawans, & Domes, 2009). In animal studies, mainly on rodents, oxytocin has been demonstrated to down-regulate aggression, but also to act on the amygdala and reduce fear (Heinrichs et al., 2009). The central nucleus of the amygdala has receptors for both oxytocin and arginine vasopressin. It seems like stimulation of these receptors inhibit the amygdala and thus oxytocin diminish fear responses by inhibiting outgoing signals to other parts of the fear system. This has been demonstrated in fMRI studies of oxytocin administration in conjunction with threatening visual stimuli (Charuvastra & Cloitre, 2008). In addition to other social functions, oxytocin and arginine vasopressin also seem to link the dopamine reward system to social bonding events, the same system that has been indicated to be dysfunctional in PTSD patients (Charuvastra & Cloitre, 2008).

Oxytocin has been demonstrated to significantly improve recognition of positive facial expressions, regardless of sex (Marsh et al., 2010). The effect was especially pronounced for subtle emotional expressions, which counters the study by Bedi et al. (2010), which indicated that MDMA decreases detection of subtle emotional signals. However, an

earlier study by Bedi et al., (2009) did not find any alterations in emotional recognition after

MDMA administration. Other effects of oxytocin include enhancing encoding of positive

memories (Guastella, Mitchell, & Mathews, 2008), suppressing subjective distress and

cortisol responses to stress (Charuvastra & Cloitre, 2008), and reducing social anxiety (Marsh

et al., 2010).

Administrating oxytocin has also been demonstrated to increase interpersonal trust

and generosity (Marsh et al., 2010). Facial features associated with trustworthiness are often

classified as happy expressions, which means that the effect oxytocin has on detecting

positive emotions may contribute to increasing trusting behaviour (Marsh et al., 2010). This

study also revealed that participants receiving oxytocin not only improved accuracy for

detecting happy expressions, but also improved in detecting other emotional expressions

(Marsh et al., 2010). Additionally, high levels of trust are associated with decreased activity

in the amygdala (Marsh et al., 2010).

That MDMA induces oxytocin and vasopressin release was first discovered in rats. In

rats MDMA has been demonstrated to induce oxytocin release following stimulation of 5-

HT_{1A} receptors in the hypothalamus as well as raising plasma levels of oxytocin. MDMA has

also been demonstrated to bind to oxytocin receptors in rats and increase cuddle behaviour

(Thompson et al., 2007). Therefore it seems likely that the release of oxytocin promotes the

prosocial effects of MDMA. In rodents MDMA administration produces higher changes in

neural activation when in a social context compared to when MDMA was administered to

lone rats (Thompson, Hunt, & McGregor, 2009). That MDMA induces release of oxytocin

also in humans was later confirmed in a study on recreational Ecstasy users (MDMA content

confirmed by urinary analysis) that measured levels of oxytocin pre- and post-clubbing

(Wolff, 2005). Subsequently this was also corroborated by clinical studies (Hysek et al.,

2012).

Hysek et al. (2012) investigated whether MDMA; like oxytocin was demonstrated to in earlier studies (Marsh et al., 2010), would selectively enhance mind-reading (the ability to infer others' attitudes, perceptions, or opinions) for positive stimuli. In addition to increasing levels of oxytocin and cortisol, MDMA was demonstrated to enhance mind-reading of positive stimuli and impair mind-reading of negative stimuli. Unlike when administrating oxytocin, however, there were no sex differences in alteration of mind-reading capability (Hysek et al., 2012). This could be explained by the increase in plasma levels of vasopressin MDMA also induces (Wolff, 2005), since vasopressin has similar effects on men as oxytocin have on women. Hurlemann et al. (2010) however demonstrated that oxytocin also increases emotional empathy in healthy males.

Reducing subjective distress and facilitating social closeness seem like especially beneficial effects for PTSD patients. These patients often feel disconnected from their therapist, friends and family. The inability to maintain close social bonds likely helps maintain the PTSD (Charuvastra & Cloitre, 2008; Johansen & Krebs, 2009). The improved social functioning can also contribute to a strong therapeutic alliance, which is essential for successful therapeutic outcome. Hysek et al. (2012) also suggest that the alteration in perception of emotional stimuli following MDMA administration could contribute to the therapeutical process. On the other hand, MDMA also induce release of vasopressin (Wolff, 2005), which has been indicated to impair extinction learning (Myers & Davis, 2006).

Some of the effects of MDMA might seem counterintuitive to treating PTSD, such as the physiological effects that seem to be a stress response. For context-dependent extinction learning to work it is important to access the memory while keeping a high emotional engagement. Even though some of the effects of MDMA seem, in isolation, to be stress-related, this does not feel as such for the patient. Instead the patient feels calm, safe, and relaxed. It is this combination of emotional engagement and relaxation induced by the

complex effects of MDMA administration that probably makes it an effective treatment for

PTSD. It is thus important to remember the complexity of neural functioning, and not focus

on individual effects or systems.

Discussion

Only limited space in this essay has so far addressed the question of adverse psychological

effects and potential neurotoxicity. As phase two studies have been approved, one could

conclude that the issue is resolved. My impression is that this topic is still debated by

researchers in the field, and that there are no conclusive answers. In this final section an

overview of the controversy concerning neurotoxicity and potential adverse sequelae of

MDMA administration will be presented, as well as implications from the completed studies,

and the final conclusion.

Neurotoxicity and Adverse Psychological Effects

The issue of whether small amounts of MDMA are neurotoxic is important to

therapeutic use for obvious ethical reasons. Because of these ethical reasons, experiments on

the potential neurotoxicity in human subjects naive to MDMA have not been allowed. Thus

almost the only option to investigate the matter has been animal studies and prospective

studies on recreational Ecstasy users (Curran, 2000).

Most studies on the neurotoxicity of MDMA have been done on animal species,

ranging from rodents to primates. These studies indicate that MDMA is neurotoxic if

administered in either very high doses or successive moderate to high doses (Green et al.,

2003; Parrott, 2001). If these results are translatable to humans are debated. Some believe it is

so, especially in conjunction with data from studies on heavy, long-term recreational users of

Ecstasy that have reported cognitive deficits and mood disorders (e.g., Halpern et al., 2004;

McCann, Mertl, Eligulashvili, & Ricaurte, 1999; Parrott, 2001). Then there are others that

find these assumptions questionable. Animal studies have been criticized for being

methodologically flawed; because researchers have been using extremely high doses for

many days in a row, as well as the complications of translating results from one species to

another. Pertaining to this debate is an interesting find by Vollenweider et al. (2001): in some

respects MDMA seems to produce opposite effects on the serotonergic system in humans

versus rodents. While the clearest example is on sensorimotor gating, this elucidates that

interspecies translation may not always be entirely straightforward.

McCann et al. (1999) claim that MDMA is neurotoxic in recreational doses. They

studied 14 people with self-reported Ecstasy use (abstinent for 3 weeks) and 15 controls (no

Ecstasy use) with positron emission topography. The Ecstasy-users exhibited decreased

global and regional 5-HT-binding compared to the controls. The degree of decrease was

correlated with extent of Ecstasy use (McCann et al., 1999). Measurements of CSF from the

spinal cord indicated that the Ecstasy using group had a lower concentration of 5-HIAA than

controls (McCann et al., 1999). Other studies measuring levels of 5-HIAA in the CSF has

however failed to replicate McCann et al.'s results (Iversen, 2006). Criticism has also been

directed at McCann et al.'s studies for conflicts of interest as well as for unsound statistics

(Iversen, 2006) and profound methodological problems (Curran, 2000; Kish, 2002).

Furthermore, some argue that moderate doses of MDMA do not lead to loss of 5-HT

terminals, nor to significant decreased 5-HT content or 5-HIAA, and also that decreases of 5-

HIAA in the CSF does not indicate neurodegeneration (Vollenweider, Gamma, Liechti, &

Huber, 1999).

Studies on heavy, long-term users have also received criticism (e.g., Curran, 2000;

Lyvers & Hasking, 2004; Vollenweider et al., 1999) for not accounting for confounding

variables such as impurity of Ecstasy, participants co-use of illicit and licit drugs, too short

periods of abstinence preceding the studies, and preexisting mental problems (Curran, 2000;

Jager et al., 2007a). Analyses of Ecstasy tablets however indicate that most tablets do contain

MDMA, but also that other agents are frequently intermixed, especially caffeine,

amphetamine, ephedrine, ketamine, and paracetamol (Parrott, 2004).

Morgan (2000) conducted a review of studies that report that recreational Ecstasy users

are more likely to suffer from psychiatric disorders, ranging from obsessive-compulsive

disorders, flashbacks, panic attacks, and psychosis, to depression. Several difficulties with

these case reports and studies are mentioned; confounding variables such as the necessary

retrospective design, subjects poly-drug use, the frequency of these disorders in the general

population, and the bias of people with psychological problems to use drugs (Morgan, 2000).

Some studies of heavy recreational Ecstasy users report impairments in cognitive functions

such as memory and learning; psychological problems like elevated anxiety, depressed mood,

sleep disorders, greater impulsivity and aggression, compared to controls. These effects have

only been found in chronic, heavy users, with relatively short periods of abstinence prior to

investigation. No residual effects have been found in light users (Jager et al., 2007b; Morgan,

2000). A review article that analysed effect of drugs on neurophysiological performance

report that adverse effects of Ecstasy-use were only present in heavy users (>50 occasions),

all of whom were poly-drug users (Fernández-Serrano, Pérez-García, & Verdejo-García,

2010).

A correlation between depression and Ecstasy use has been found in several studies.

These are however retrospective and can not determine a causal relationship between Ecstasy

and depression. Huizink (2006) found a possible temporal pathway when they demonstrated

in their prospective population study that symptoms of anxiety and depression in children and

adolescents (guaranteed to predate Ecstasy-use) accurately reflected subsequent Ecstasy use

as young adults; anxious and/or depressed children were more likely to have used MDMA as

adults. This led the authors to the conclusion that using MDMA could be for self-medicating

purposes. Majumder, White, and Irvine (2012) corroborated these results in a study that found that MDMA significantly improved depressive symptoms in, otherwise healthy, volunteers.

There are a few case studies published that report of severe detrimental effects, including psychosis, occurring after a single dose of Ecstasy (e.g., Masi, Mucci, & Floriani, 2002; McCann & Ricaurte, 1991; Potash, Gordon, & Conrad, 2009; van Kampen & Katz, 2001). However, in none of these studies did toxicology measures confirm presence of MDMA, thus attribution of the problems to MDMA was solely based on the patients' self-reported Ecstasy use (Cole & Sumnal, 2003). Furthermore, as Curran (2000) points out, most of these reports are of single cases and nearly all subjects were poly-drug users, often with other vulnerability factors; so a direct link between MDMA use and subsequent psychiatric problems was not confirmed. Iversen (2006) points out that these are very few incidents compared to the estimated 10-28 million users worldwide (UNODC, 2012).

Concern has also been voiced about the abuse potential of MDMA. A meta-study by Degenhardt, Bruno, and Topp (2010) reviewed evidence from animal- and human studies in regard to MDMA/Ecstasy dependence. They concluded that the physiological basis for MDMA dependence is weak, although not nonexistent, but that the psychological aspects make a greater contribution to the risk of escalating use than physiological dependence (Degenhardt et al., 2010). The outcome of Mithoefer et al.'s (2012) study also points in the direction that fear of later MDMA abuse may be ungrounded. No illicit drug use, besides incidental use of cannabis (of equal frequency as pre-study), was reported in participants subsequent to participation.

Implications From Contemporary Studies

The finished studies of MDMA-assisted psychotherapy for PTSD demonstrate

impressive results. They do however have several limitations that will hopefully be addressed in future studies. These limitations include small sample sizes, uneven sex and ethnic distribution (majority females, all Caucasian); as well as difficulties maintaining blindness to experimental conditions throughout the study. Although the studies were designed double-blind, with independent raters who remained blind, most participants correctly guessed their assignment. This was addressed in Oehen et al.'s (2011) study, which included an active placebo, but complete blindness was not accomplished there either. Furthermore, additional sessions of (non-drug) psychotherapy were more common in the MDMA groups than in the placebo groups, but since CAPS scores were taken before additional psychotherapy sessions took place, this did not affect clinical response outcome.

The follow-up study by Mithoefer et al. (2012) is interesting in many aspects. Firstly, long-term follow-up studies of PTSD are rare and mostly confined to months after treatments. Secondly, the efficacy is quite striking. The participants in the original study had lived with treatment-resistant PTSD for a mean of 19 years prior to enrolment. After the mean lapse of 3,5 years after the 2 to 3 sessions of MDMA-assisted psychotherapy, all participants reported significant decreases in CAPS scores as well as increased quality of life. The unusually long follow-up period (at most 5 years) indicates that despite the likely occurrence of life events, positively or negatively affecting the subjects' mental health, the MDMA-treatment had a significant and long-lasting impact. This is indicated not only through statistical measures of the standardized questionnaires, but also through the participants' comments; which describe the treatment as helpful (e.g., "the therapy made it possible for me to live"), difficult (e.g., "one of the toughest things I have ever done"), as a step in an on-going process, and also how the participants experienced the MDMA-assistance of psychotherapy (e.g., "It increased my ability to stay with and handle getting through my emotions") (Mithoefer et al., 2012).

The therapeutic alliance has been identified as the most important factor in

psychotherapy outcome for PTSD patients, the influence has been reported to be twice as large for PTSD patients as for other patients with psychopathology (Charuvastra & Cloitre, 2008). Therefore it seems reasonable to stress the importance of strengthening this relationship in treating PTSD even more than has been done in completed studies. One suggestion could be to administer oxytocin in pre-MDMA-psychotherapy sessions to facilitate the social bonding between the patient and the therapist.

In sum, these studies indicate that incidental use of moderate doses of MDMA is safe and well tolerated. In the controlled clinical setting few, if any, of the adverse effects associated with recreational use of Ecstasy should appear. Moreover, if negative experiences arise, the trained team of psychotherapists and medical staff available will be able to adequately address those issues.

Conclusion

The aim of this essay was to investigate the neurobiological rationale of treating PTSD with MDMA. Johansen and Krebs (2009) suggested that the effects of MDMA on norepinephrine, cortisol, oxytocin, vmPFC activity, and amygdala activity are the main mechanisms that make PSTD treatment with MDMA effective. In this essay these claims have been investigated. Regarding oxytocin and regulation of activity in amygdala and vmPFC their claims seem to be well grounded in the empirical data. MDMA decrease activity in areas associated with fear, most notably the amygdala, which exhibit increased activity in PTSD patients. MDMA also increase activity in the vmPFC, which in PTSD patients exhibit decreased volume and activity. This means that MDMA may normalize activation in areas displaying abnormal activity in PTSD patients. MDMA also affect areas, such as the ventral striatum, that while they have not been demonstrated as abnormal in PTSD patients, may still be beneficial for these patients. The MDMA propagated release of

oxytocin is well studied and seems to have a significant positive impact on the therapeutic

process with its effect on trust and sociability, which benefits the PTSD patients.

Regarding cortisol and norepinephrine the conclusions are less clear. MDMA seems to

affect serotonin to a much higher degree than norepinephrine, even though serotonin help

regulate levels of norepinephrine, and thus lower anxiety induced by high levels of

norepinephrine. Since serotonin regulate mood and co-morbid depression is common among

PTSD patients, it seems plausible that treating the depression also helps the patient, even

though the increased serotonin may not treat the PTSD per se. Some studies indicate that

PTSD patients have decreased levels of cortisol, and MDMA has been demonstrated to

increase circulating cortisol. Whether this has any significant impact on the therapeutic

effects on PTSD needs to be further investigated.

I think that it is important to emphasise the complex interactions of different neural

systems that MDMA seems to induce. If viewing effects separately, it might for example

seem illogical to try to treat an anxiety disorder with a substance that can elicit physiological

stress responses. This stress response is however beneficial for extinction learning, because

the patient does not feel stressed or anxious; but safe and calm. Exactly how all the different

systems interact and produce the beneficial effects for PTSD patients remains to be studied in

detail in future empirical research.

The empirical data seem rather clear on the subject of neurotoxicity. While repeated

administration and/or high doses do have detrimental effects on the serotonergic system,

incidental use of moderate doses such as those used in the clinical settings have no detectable

or measurable adverse sequelae. My conclusion is that the empirical data examined support

that treating PTSD with MDMA is rational from a neurobiological position, as well as

reasonably safe, and shows promising efficacy.

I think that the phase three studies will be interesting to follow as these may provide the

basis for implementation of a well-needed treatment method for a previously chronically ill patient group. Phase three studies will also supply further empirical data regarding potential adverse long-term effects. In the future less invasive or inconvenient methods of neuroimaging may provide clearer data on what exactly is happening in the brain when undergoing MDMA-assisted psychotherapy.

If the phase three studies demonstrate as efficient and safe results as the phase two studies, it would also be interesting to investigate the potential of treating other anxiety disorders and depression with MDMA. Perhaps one starting point would be to investigate its therapeutic effects on patients suffering from social anxiety. Because of the increased sociability, talkativeness and openness, couples therapy would also be an interesting avenue to explore. Another viable research topic could be, as Scahill and Anderson (2010) also proposes, treating autism with MDMA. The effects of MDMA seem to overlap the difficulties experienced by individuals with high-functioning autism. MAPS offer a research grant for a pilot study on this topic, and are currently gathering anecdotal reports in order to facilitate developing protocols (MAPS, 2011).

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