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A Systematic Literature Review of the Effects of MDMA on Social Cognition – Implications for Couple Therapy

Ana Miranda

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Universidade do Porto
Faculdade de Psicologia e de Ciências da Educação

A SYSTEMATIC LITERATURE REVIEW OF THE EFFECTS OF MDMA ON SOCIAL COGNITION – IMPLICATIONS FOR COUPLE THERAPY

Ana Maria da Cruz Miranda
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Agradecimentos

"É justamente a possibilidade de realizar um sonho que torna a vida interessante."

-Paulo Coelho (1988, O Alquimista)

À minha mãe, ao meu pai, ao Afonso e à Laura, obrigada por tornarem este sonho tangível.

" I understood that our entire universe is contained in the mind and the spirit. We may choose not to find access to it, we may even deny its existence, but it is indeed there inside us, and there are chemicals that can catalyze its availability. MDMA, it was beginning to be apparent, could be all things to all people."

- Alexander Shulgin and Ann Shulgin (1991, Pihkal: A Chemical Love Story)

Resumo

Objetivo. A reconhecida molécula psicoativa MDMA é considerada um potente catalisador de envolvimento social e sentimentos empáticos. As suas qualidades sociocognitivas únicas potencializam-na como um adjuvante da psicoterapia, especialmente no contexto da terapia de casal. Assim, o objetivo desta revisão sistemática é clarificar os efeitos da MDMA na cognição social em indivíduos saudáveis. Com base nestes resultados, pretendemos também discutir uma perspetiva integrativa sobre a sua relevância e potenciais benefícios na terapia de casal.

Método. Foi efetuada uma pesquisa sistemática nas bases de dados PubMed, Web of Science e EBSCO. As publicações foram selecionadas desde 2000 até ao presente. Após a remoção de duplicados, os estudos foram selecionados e os dados extraídos utilizando critérios de exclusão e inclusão pré-definidos. Apenas foi considerada a administração de medidas objetivas da função social.

Resultados. Treze artigos foram incluídos, mostrando os efeitos significativos do MDMA em construtos sociocognitivos. Tanto a empatia emocional como a generosidade foram melhoradas. Demonstrou-se igualmente uma redução na sensibilidade à rejeição e na estimulação a sons negativos. Relativamente ao reconhecimento de emoções, confiança e cooperação, os resultados são ainda inconsistentes, sugerindo que a droga pode não afetar consistentemente estes aspetos da interação social.

Conclusões. Os resultados mostraram a escassez de literatura que examina os efeitos sociocognitivos do MDMA. Todavia, foram encontrados efeitos relevantes aparentemente benéficos para o contexto da terapia de casal, embora este campo ainda não esteja devidamente estudado. Estudos futuros são essenciais para aprofundar os efeitos do MDMA na cognição social e o seu poder terapêutico em casais.

Palavras-chave: *Cognição social; Adultos saudáveis; MDMA; Terapia de casal; Revisão sistemática*

Abstract

Aim. MDMA is a widely used psychoactive molecule that is recognized as a potent catalyst for social engagement and empathetic feelings. Its unique socio-cognitive qualities potentiate it to adjunct psychotherapy, especially in the context of couple therapy. Thus, the aim of this systematic review is to clarify the effects of MDMA on social cognition in healthy individuals. Based on these findings, we also want to discuss an integrative perspective on its relevance and potential benefits in couple therapy.

Method. A systematic search was performed in the PubMed, Web of Science, and EBSCO databases. Publications were narrowed down from 2000 to the present. After removing duplicates, the studies were selected, and data extracted using pre-defined exclusion and inclusion criteria. Only the administration of objective measures of social function was considered.

Results. Thirteen articles were included, showing MDMA's significant effects on cognitive social constructs. Both emotional empathy and generosity were enhanced. MDMA also reduced the rejection sensitivity and the arousal to negative sounds. Regarding emotion recognition, trust, and cooperation, the findings are still inconsistent, suggesting that the drug may not consistently affect these aspects of social interaction.

Conclusion. The outcomes exhibited the scarcity of literature examining the cognitive social effects of MDMA. However, relevant effects were found that seem to be very beneficial for the context of couple therapy, although this field is not yet properly studied. Future studies are essential to deepen the effects of MDMA on social cognition and its therapeutic power in couples.

Keywords: *Social cognition; Healthy adults; MDMA; Couple therapy; Systematic review*

Introduction

Social cognition is a fundamental construct for our understanding of human interaction. As argued by Shany-Ur and Rankin (2014), it encompasses a dynamic interaction of rapid and emotional mechanisms influenced by individual attitudes, preconceptions, and personality traits, which contribute to the attribution of meaning and emotional significance to social stimuli. These mechanisms converge with acquired social knowledge and higher-order reflective reasoning about the thoughts and intentions of others, culminating in the capacity for cognitive empathy and theory of mind.

Moreover, as pointed out by Beaudoin and Beauchamp (2020), social cognition extends to a complex set of mental capacities essential for the perception, interpretation, and response to social and emotional stimuli, serving as a foundation for the development of social competence and adaptation. In brief, adaptive social behavior is the product of the interdependent functioning of socio-affective and socio-cognitive processes (i.e., executive functions, in particular, the hot executive processes), and its analysis in psychotherapeutic context is of greater relevance when dealing with issues connected to disruptions in social interaction.

MDMA (±3,4-methylenedioxymethamphetamine), also known as "ecstasy", "molly" or "XTC", is a widely used synthetic, psychoactive molecule that, apart from its stimulating nature, is recognized as a potent catalyst for social engagement and empathetic feelings – also earning the classification of "empathogen" or “entactogen” (Frye et al., 2014; Hyseck et al., 2014). In fact, it is the substance most widely studied in relation to social perception (Preller & Vollenweider, 2019).

The effects of MDMA, when administered orally, become apparent 30-45 minutes afterward, peaking 90-120 minutes later. Specifically, in a laboratory context, MDMA has been shown to improve subjective, cognitive, and emotional measures of social processing. This drug produces subjective prosocial feelings, decreases feelings of fear and defensiveness, and increases positive mood states, as well as empathy and feelings of friendliness and interpersonal closeness (Baggott et al., 2016; Kirkpatrick et al., 2014). The current evidence on the psychological impact of MDMA thus points to the reasons why this substance is used within the recreational context, and to a unique social behavioral profile of this molecule (Bedi et al., 2010; Kirkpatrick et al., 2015), turning it into a potential experimental adjunct to psychotherapy.

Although more research is needed, these effects of MDMA may be neuro-pharmacologically linked to the increased release of oxytocin (Kirkpatrick et al., 2014). As shown in some pharmacological studies, MDMA increases not only the plasma levels of oxytocin, but also of cortisol and prolactin compared with placebo (Dolder et al., 2018; Hyseck et al., 2014). Moreover, this molecule also releases serotonin (Hyseck et al., 2012; White et al., 1996) and norepinephrine in the brain (Hyseck et al., 2014; Verrico et al, 2007). These hormones and neurotransmitters are associated with essential aspects of interpersonal experiences of love, well-being, pleasure, and anxiety reduction – underlining MDMA's power to increase social bonding and to create positive and secure relationships (Dolder et al., 2018).

Before it was illegalized, MDMA was used and investigated in psychotherapy from 1977 to 1985 (Passie, 2018), being considered a beneficial drug by some specialist psychotherapists due to its effects (Eisner, 1989). Essentially, MDMA has been studied in laboratory control since 2000, specifically in the treatment of post-traumatic stress disorder (PTSD; Bouso et al., 2008; Mithoefer et al., 2013; Oehen et al., 2013); and, more recently, in the treatment of social anxiety related to life-threatening illnesses and to autism (de Wit & Bershad, 2020; MAPS, n.d.), and in the context of eating disorders (MAPS, n.d.). However, MDMA was first identified as a therapeutic treatment for couple therapy (Wagner et al., 2021) and has been used in this field since it was first applied in 1970 (Greer & Tolbert, 1986; Passie, 2018). With this, it is important to emphasize the idea that MDMA-assisted couple therapy is not new or innovative and, if it were to be characterized, it would be more accurate to say that we are facing an era of renaissance of this type of therapy.

In fact, the empathogenic and interconnectedness qualities of MDMA can be essential for promoting a therapeutic opportunity in the context of couple therapy (Wagner et al., 2021). Couple therapy is concerned with the interaction patterns between two individuals, taking into account each member's personal history and input, and is often applied to treat problems such as sexual dysfunction, disclosure of infidelity, depression, anxiety disorders, addiction, infertility, serious medical illnesses, and parental incongruences (Fishel & McKeon, 2008). Thus, through MDMA-assisted therapy and the social profile of this empathogen, couples can feel more comfortable sharing their emotions, as well as addressing issues with less difficulty (Wagner et al., 2019), which is particularly useful for dealing with tension and communication between couples. However, the literature on MDMA-assisted therapy for couples is still scarce, being mainly centered on the context

of PTSD. Actually, a phase 2 trial of MDMA-assisted cognitive processing therapy for PTSD is ongoing (National Library of Medicine, 2023; Remedy Center Institute, n.d.).

Overall, anecdotal and experimental data indicate that MDMA produces potentially therapeutic acute socioemotional effects. Nevertheless, the basic emotional processes underlying its prosocial effects (Wardle & de Wit, 2014) have yet to be established, as well as the mechanism by which MDMA can improve psychotherapy outcomes (Borissova et al., 2021). For these reasons, the aim of this systematic review is to clarify the effects of MDMA on social cognition, when objective measures of social function are applied. Additionally, based on these findings and recent literature on the effects of MDMA in couple therapy, we want to discuss an integrative perspective on its relevance and potential benefits in the therapeutic context, specifically in couple therapy.

Method

The following systematic review conforms with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021).

1. Data Sources and Search Strategy

A systematic research was conducted between August and early September 2023, using the following databases: PubMed, EBSCO (Academic Search Ultimate, APA PsyInfo, APA PsycArticles, and Psychology and Behavioral Sciences Collection), and Web of Science. The time frame of the publications was restricted from the year 2000 to the present, with no language restrictions. The final search string was based on the combination of the following keywords: ((“MDMA” OR “ecstasy” or “methylenedioxymethamphetamine”) AND (“social cognitive effects” OR “social cognition” OR “social behavio*” OR “social interaction” OR “empath*” OR “theory of mind” OR “emotional recognition”)). No additional articles were included in the manual search.

2. Eligibility Criteria

To consider inclusion, the studies had to meet the following criteria: (1) publication between 2000 and 2023 in peer-reviewed journals; (2) English or European or Brazilian Portuguese must be the language of publication; (3) participants aged 18 years or older; (4) non-randomized or randomized clinical trials; (5) studies with healthy individuals with or

without previous MDMA experience; (6) must include the administration of at least one objective neuropsychological instrument to examine the acute effects of MDMA on social cognition; and (7) must include in the results an objective analysis of the latter effects.

The exclusion criteria were justified by: (1) qualitative studies, literature reviews, systematic reviews, meta-analyses, and grey literature; (2) unavailability of the abstract; (3) animal studies; (4) studies with children and/or adolescents; (5) studies that do not address the social cognitive effects of MDMA; and (6) focus only on molecules other than the central target of the present review.

3. Study Selection

The acquired references were imported into the Rayyan platform (Ouzzani et al., 2016) to eliminate duplicate entries and conduct a preliminary screening based on the criteria for inclusion and exclusion, primarily by reviewing the titles and abstracts. Subsequently, employing Mendeley as a reference management tool, a comprehensive assessment of the full texts of the remaining studies was undertaken, with inclusion contingent upon meeting predetermined criteria. The entire selection process was conducted autonomously by two reviewers, denoted as AM and LR. The outcomes of each analysis were subsequently compared and deliberated upon. The two independent researchers exhibited a high degree of agreement, as evidenced by Cohen's kappa coefficient ($\kappa = 0.76$), indicating strong concordance in their assessments.

4. Data Extraction

After reaching a consensus on the articles to be included, we proceeded to gather data using a Microsoft Excel spreadsheet. The collected information covered: (1) study identification details (e.g., authors, year of publication, location); (2) sample characterization (e.g., sample size, mean age, sex distribution, level of education, body mass index (BMI), history of MDMA use, psychiatric assessment); (3) outcome of interest (e.g., empathy) and the neuropsychological instrument applied to evaluate it (e.g., Multifaceted Empathy Test, MET). Eligibility criteria considered studies prioritizing the social cognitive effects in the healthy population under the influence of MDMA, with a focus on various assessment time points if applicable; (4) study design; (5) intervention features (e.g., organization, MDMA dosage, frequency, comparator details, setting); and (6) relevant findings, limitations, and future research directions. There was no need for direct communication with the study investigators.

Results

1. Search results

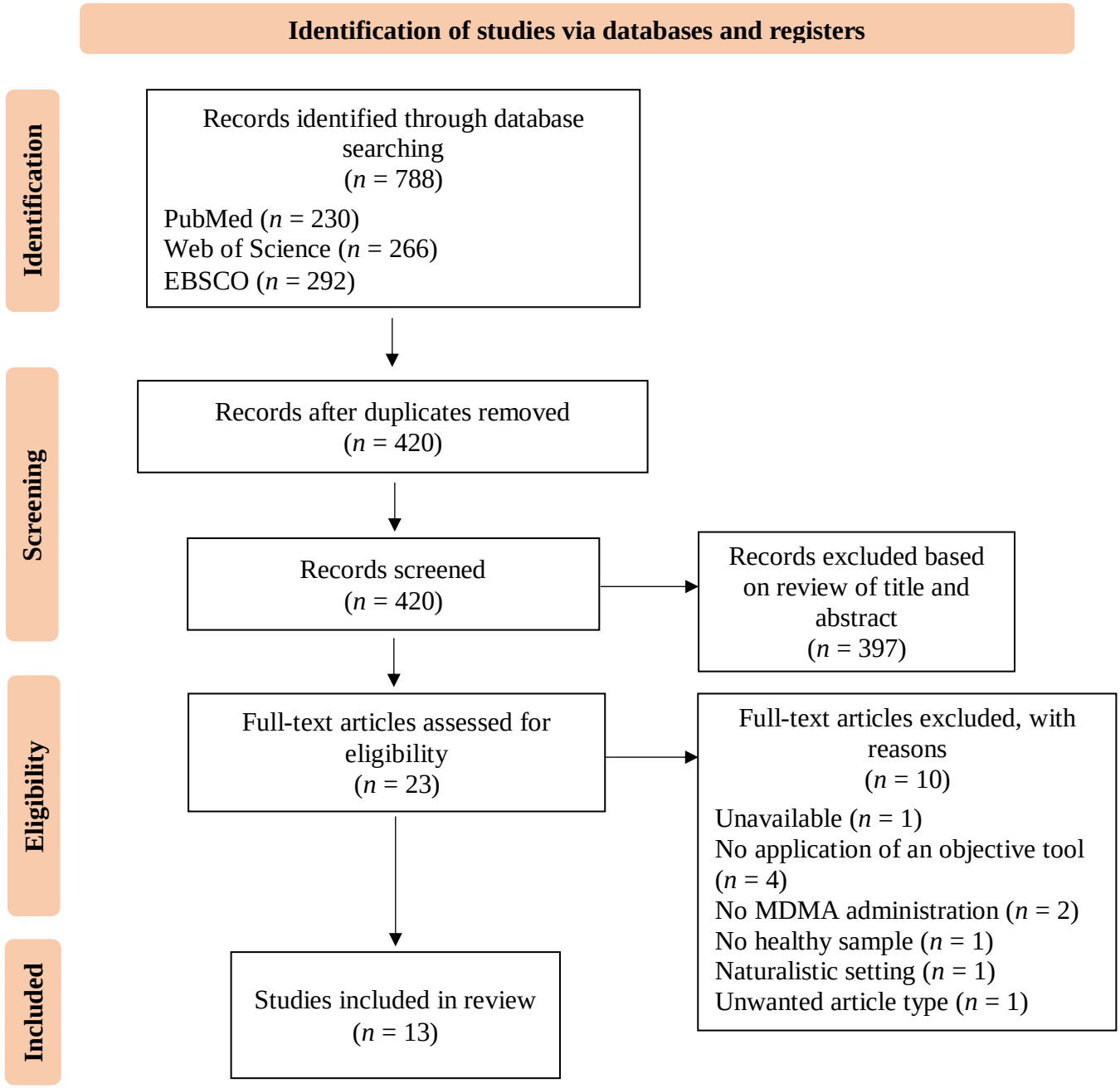
The information presented below regarding the study selection process is aligned with the data provided in the PRISMA diagram (see Figure 1).

From a search of 788 articles, found in the PubMed, Web of Science, and EBSCO databases, 368 articles were removed due to duplication, leaving a total of 420 articles to be screened. Subsequently, upon reviewing the titles and abstracts, 397 articles that failed to meet the inclusion criteria, were excluded.

Of the remaining publications, a total of 23 results were assessed for eligibility, 10 of which were excluded because they did not meet inclusion criteria. Of these 10, four did not address any objective task, two did not contemplate the administration of MDMA, one did not have the full article available, one did not use a healthy sample, one was done in a naturalistic setting and, finally, one did not correspond to the desired article type. Therefore, a total of 13 relevant articles were found that were included in this systematic review (see Figure 1). Six studies were conducted in the USA (Bedi et al., 2010; Doss et al., 2018; Frye at al., 2014; Kirkpatrick et al., 2014; Kirkpatrick et al., 2015; Wardle & de Wit, 2014), three in the UK (Borissova et al., 2021; Gabay et al., 2018; Gabay et al., 2019), two in Switzerland (Hyseck et al., 2014; Schmid et al., 2014) and two in the Netherlands (Kuypers et al., 2014; Kuypers et al., 2018). All of them are written in English. Most of the articles were published in 2014 (n = 6), secondly in 2018 (n = 3), and one in each of the following years: 2010, 2015, 2019, and 2021. The characteristics of the studies included in this review are organized in Table 1 (see Appendixes).

Figure 1

PRISMA flow diagram of the selection of studies.



2. Sample Characterization

All 13 studies included healthy samples, enrolling a total of 418 subjects. The sample ranged from a minimum of 20 (Gabay et al., 2019; Kuypers et al., 2014; Kuypers et al.,

2018) to a maximum of 65 participants (Kirkpatrick et al., 2014). The participants ages ranged from 18 to 58 years old. For more details see Table 1.

Within the scope of this comprehensive analysis, the number of females in each study varied significantly, with notable differences observed. Specifically, five studies (Doss et al., 2018; Frye et al., 2014; Hysek et al., 2014; Schmid et al., 2014; Wardle & de Wit, 2014) presented a balanced sample size in terms of the participants' sex, with half of each sample being female. In contrast, two studies (Gabay et al., 2018; Gabay et al., 2019) exclusively enrolled male participants. Furthermore, the study by Kirkpatrick et al. (2015) featured a very low sample of females (n=9) compared to the males (n=23), highlighting a noteworthy sex imbalance. Similarly, Borissova et al. (2021) included only seven female subjects of a total of 25. The studies by Kuypers et al. (2014) and Kuypers et al. (2018) predominantly included male participants (N=20, $n_{females}$=8 in both), along with Bedi et al. (2010)'s study in which only nine females were included (N=21). Finally, Kirkpatrick et al. (2014) featured a larger sample size (N=65) but still had a low proportion of females (n=25). Regarding the participants' level of education, see Table 1.

Diversity in BMI was evident across the studies under scrutiny. Six investigations reported specific BMI ranges, such as 18.5–30 kg/m² (Bedi et al., 2010), 18-30 kg/m² (Kirkpatrick et al., 2014; Kirkpatrick et al., 2015), 19-30 mg/m² (Frye et al., 2014; Wardle & de Wit, 2014) and 18-27 kg/m2 (Schmid et al., 2014). In one case, the BMI differed among study groups. Doss et al. (2018) reported a slightly higher BMI in the MDMA Encoding group (M=24.37 kg/m²) compared to the Retrieval group (M=23.32 kg/m²). The remaining six studies did not provide BMI data, leaving this crucial parameter undescribed (Borissova et al., 2021; Gabay et al., 2018; Gabay et al., 2019; Hysek et al., 2014; Kuypers et al., 2014; Kuypers et al., 2018). Moreover, although it does not describe BMI, the study conducted by Kuypers et al. (2014) included participants with a mean weight of 70.25 kg (SD=13.09).

Lifetime experience of MDMA use among participants showed considerable variability between studies, with largely elevated standard deviations. Both Kirkpatrick et al. (2015) and Kuypers et al. (2018) recruited samples with similar average MDMA experience with high standard deviations: 17.0 times (SD=19.3) and 16.8 times (SD=23.2), respectively, suggesting remarkable variability in lifetime use of the drug. Two investigations reported a lower average lifetime consumption of MDMA, which consisted of 15.0 times (Bedi et al., 2010; Kirkpatrick et al., 2014), but also with high standard deviation values – 23.1 and 11.2, respectively. In contrast, both Kuypers et al. (2014) and Wardle & de Wit (2014) not only exhibited close values of average MDMA experience, but

also comparable standard deviations [10.95 times (*SD*=8.97) and 10.2 times (*SD*=8.2), respectively]. Differently, in Doss et al. (2018), varying MDMA experience levels were presented between different experimental groups. The Encoding group reported an average of 15.95 times (*SD*=0.47), while the Retrieval group had a lower average of 10.98 times (*SD*=0.41).

Conversely, six studies did not provide explicit data on the average values of MDMA experience. In the study by Frye et al. (2014), it is only mentioned that all participants had an experience with MDMA, with 25 subjects having consumed it between one and 10 times, and 11 subjects between 11 and 50 times. Similarly, although they did not specify the exact number of times participants used MDMA, Gabay et al. (2018) and Gabay et al. (2019) only included experienced participants with at least one previous experience with MDMA. In contrast, Borissova et al. (2021) did not include only experienced individuals, but the majority were experienced (21 individuals out of 25), ranging incredibly from 1 to 200 times (Median=10, IQR=3-45). In Hysek et al. (2014), the number of experienced subjects is already notably lower, consisting of 10 individuals (N=32), with less than five reported intakes. In the same sense, Schmid et al. (2014) reported that only eight subjects (N=30) had experience with MDMA, although they did not provide a specific number of times. The heterogeneity in relation to this variable is truly substantial.

Psychiatric evaluations were carried out in nine studies, and details have been provided in eight of them. Five studies have conducted a structured clinical interview (Bedi et al., 2010; Frye et al., 2014; Gabay et al., 2018; Schmid et al., 2014; Wardle & de Wit., 2014). The modified Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV; Frye et al., 2014; Wardle & de Wit., 2014), the Mini-International Neuropsychiatric Interview by Sheehan et al. (1998) (Gabay et al., 2018), and the Structured Clinical Interview for DSM-IV (Schmid et al., 2014) were implemented. Bedi et al. (2010) refer that the subjects were screened according to the DSM-IV Axis 1 diagnosis, including substance dependence. Meanwhile, Doss et al. (2018) conducted a semi-structured psychiatric interview. Two studies only explained that was carried out an initial telephone and in-person psychiatric evaluation (Kirkpatrick et al., 2014), or an in-person psychiatric evaluation (Kirkpatrick et al., 2015). Borissova et al. (2021) executed a psychiatric interview, but specific information on it is lacking. No specific method of psychiatric assessment was reported in four studies, which mentioned that the participants did not have a psychiatric illness (Gabay et al., 2019; Hyseck et al., 2014) or that they were healthy (Kuypers et al., 2014; Kuypers et al., 2018).

3. Study Design and Intervention Characteristics

The research design was mostly uniform (see Table 1). All 13 experiments were double-blinded and placebo-controlled. Eight out of the 13 studies used a randomized design (Bedi et al., 2010; Doss et al., 2018; Hysek et al., 2014; Kirkpatrick et al., 2014; Kirkpatrick et al., 2015; Kuypers et al., 2014; Kuypers et al., 2018; Schmid et al., 2014). The remaining five studies were counterbalanced (Borissova et al., 2021; Frye et al., 2014; Gabay et al., 2018; Gabay et al., 2019; Wardle & de Wit, 2014).

A total of eight studies were conducted by a within-subjects design (Bedi et al., 2010; Borissova et al., 2021; Doss et al., 2018; Frye et al., 2014; Kirkpatrick et al., 2015; Kuypers et al., 2014; Kuypers et al., 2018; Wardle & de Wit, 2014). Four studies with a cross-over design were identified (Gabay et al., 2018; Gabay et al., 2019; Hysek et al., 2014; Schmid et al., 2014). Only one used a within-and-between-subjects design (Kirkpatrick et al., 2014).

Regarding intervention, Bedi et al. (2010) carried out a four-session study, in which participants received a capsule containing either MDMA (0.75 mg/kg and 1.5 mg/kg), methamphetamine (20 mg), or placebo, all orally administered. In another four-session study, MDMA (0.75 mg/kg and 1.5 mg/kg) was administered orally, placebo was also administered both orally and intranasally, and oxytocin (20 or 40 IU[1]) was given intranasally (Kirkpatrick et al., 2014). The study by Kuypers et al. (2014) encompassed four sessions with four treatment conditions in which a fixed dose of MDMA (75 mg), with or without pindolol (20 mg), placebo, or oxytocin nasal spray (40 IU + 16 IU) were administered, all tested orally, except oxytocin.

Additionally, four studies carried out three sessions. In the study by Kirkpatrick et al. (2015), two variable MDMA doses (0.5 mg/kg and 1.0 mg/kg) were administered, considering the participants' median weight (72.1 ± 13.1 kg), which translated to approximate doses of 36 mg and 72 mg, as well as one session of placebo, orally. Both Frye et al. (2014) and Wardle et al. (2014) applied variable doses of MDMA (0.75 mg/kg and 1.5 mg/kg) and placebo, all orally, throughout the three sessions. Schmid et al. (2014) also performed a study with three experimental sessions but using a fixed dose of MDMA (75 mg), methylphenidate (40 mg), and placebo, all orally administered.

Three of the 13 papers conducted a two-session drug application study. Borissova et al. (2021) developed a four-session study, with only two of them being acute drug administration sessions, and the others subacute sessions. In the acute sessions, participants

[1] International Unit

received a fixed dose of MDMA-HCl[2] (100 mg) and placebo (100 mg of ascorbic acid), both orally. In Gabay et al. (2019), one session involved the administration of a fixed dose of 100 mg MDMA and the other a placebo, both orally. Only Doss et al. (2018) carried out a two-session study in which was orally administered a variable dose of MDMA (1.0 mg/kg).

The remaining three studies included a single dosing session, all applying a fixed oral dose of MDMA. In Hyseck et al. (2014), participants were treated with both MDMA (125 mg) and placebo (64 assessments). As for Gabay et al. (2018), 100 mg of MDMA and a placebo was administered. Finally, Kuypers et al. (2018) also carried out a single session of oral treatment with MDMA (75 mg) or placebo. For more details see Table 2.

Additionally, six studies did not describe the research setting (Frye et al., 2014; Gabay et al., 2018; Gabay et al., 2019; Hysek et al., 2014; Kuypers et al., 2014; Kuypers et al., 2018). The remaining seven experiments provide little description of the setting. Specifically, one was performed at a university (Doss et al., 2018), three in a laboratory context (Bedi et al., 2010; Borissova et al., 2021; Kirkpatrick et al, 2014; Kirkpatrick et al., 2015; Wardle & de Wit, 2014), and one in a hospital research ward (Schmid et al., 2014).

4. Social Cognitive Domains and Tasks

The studies set out to examine different domains of social cognition, applying different cognitive tasks. The domains studied include emotional recognition (Bedi et al., 2010; Hysek et al., 2014; Kirkpatrick et al., 2014; Schmid et al., 2014; Wardle & de Wit, 2014), trust and cooperative behavior (Borissova et al., 2021; Gabay et al., 2019), social decision-making (Borissova et al., 2021), emotional memory (Doss et al., 2018), social acceptance and rejection sensitivity (Frye et al., 2014), altruistic behavior (Gabay et al., 2018), empathy (Hysek et al., 2014; Kuypers et al., 2014; Schmid et al., 2014), generosity (Kirkpatrick et al., 2015), social interaction (Kuypers et al., 2014), processing of emotional sounds and implicit attitudes (Kuypers et al., 2018), and moral judgment and theory of mind (Schmid et al., 2014).

The cognitive tasks and the timing of their administration varied significantly across the studies, reflecting a broad range of experimental approaches. Bedi et al. (2010) incorporated emotional recognition tasks such as the Facial Emotional Recognition Task (FERT), Reading the Mind in the Eyes – Revised test (RMET-R, or Eyes Test for short), and Diagnostic Analysis of Nonverbal Behavior – 2nd Edition (DANVA-2), which were

[2] MDMA hydrochloride

administered around 65 minutes post-dose. These tasks primarily focus on participants' abilities to perceive and interpret emotional cues. In the Hyseck et al. (2014) study, FERT was conducted at 120 minutes post-dose to examine emotion recognition in different social contexts. Schmid et al. (2014) also administered the FERT 75 minutes after dosing. Emotion identification was also assessed using tests such as the Morphed Facial Expression Task (mFER; Kirkpatrick et al., 2014), administered 60-120 minutes after the dose, and the Dynamic Emotional Identification Task (DEIT; Wardle & de Wit, 2014), administered between 70-110 minutes post-dose.

The study by Borissova et al. (2021) explored social decision-making processes through games like the Public Project Game, the Dictator Game, the Ultimatum Game (UG), and the Trust Investment Task, carried out approximately between 165-195 minutes post-dose, thus exploring economic behaviors, trust, and cooperation between participants. Similarly, the Trust Game, applied 120 minutes post-dose (Kuypers et al., 2014), and the UG (Gabay et al., 2018) and the Prisoner's Dilemma (PD; Gabay et al., 2019), both administered around 95 minutes post-dose, aimed to investigate cooperation and trust in social interactions, and also fairness, equity, and reciprocity.

The International Affective Picture Set task (IAPS), applied in Doss et al. (2018) around 90 minutes post-dose, involved the presentation of emotionally charged images to elicit emotional responses and thereby examine emotional memory.

Frye et al. (2014) administered the Cyberball task around 165 minutes post-dose, aiming to study social exclusion and inclusion dynamics.

To investigate empathy, Hyseck et al. (2014) administered the MET approximately 180 minutes post-dose, which involved assessing participants' empathy levels. Both Schmid et al. (2014) and Kuypers et al. (2014) also applied the MET but at different time points – 90 minutes post-dose and 105 minutes post-dose, respectively. Kuypers et al. (2014) also administered the Reading the Mind in the Eyes Test (RMET) at 105 minutes after the dose.

Other tasks comprehended the Welfare Trade-Off Task (WTT; Kirkpatrick et al., 2015) to test generosity at 90 minutes post-dose; the Processing of Affective Sounds Task (PAST), and the Approach-Avoidance Task (AAT), with the aim of examining the processing of emotional sounds and cognitive bias at 90 minutes post-dose (Kuypers et al., 2018); and, finally, the Moral Judgment Task (MJT) and the Movie for the Assessment of Social Cognition (MASC) to test morality and theory of mind (Schmid et al., 2014) at 120 and 180 minutes after the dose, respectively.

5. Social Cognitive Effects of MDMA

5.1. Emotional Recognition

MDMA's impact on emotion recognition was a focus of five studies (Bedi et al., 2010; Hyseck et al. 2014; Kirkpatrick et al. 2014; Schmid et al., 2014; Wardle & de Wit, 2014). Both Bedi et al. (2010) and Kirkpatrick et al. (2014) specifically noted a reduced accuracy in identifying angry and fearful faces, particularly under the higher dose of MDMA (Bedi et al., 2010). The latter results are in line with the observed slowed perception of angry expressions under a higher dose of MDMA by Wardle & de Wit (2014). This observation suggests that MDMA's effects on emotional processing may manifest as altered temporal perception of specific emotions, which may have implications for social interactions and emotional responses. Conversely, this impairment in recognizing fearful expressions did not extend to other emotions, as there was no effect on the identification of happy faces (Kirkpatrick et al., 2014). Moreover, there was no effect on the recognition of affective cues when they were only from the eye region or voices (Bedi et al., 2010). On the other hand, Hyseck et al. (2014) indicated an overall impairment in facial emotion recognition compared to placebo. Besides, emotional recognition was shown to be affected differently in males and females (Hyseck et al., 2014) – women showed significantly worse performance after treatment with MDMA compared to treatment with placebo, whilst no significant effect of MDMA was found in men.

5.2. Emotional Memory

The impact of MDMA on emotional memory was explored by the study of Doss et al. (2018), which found no significant effect on overall memory accuracy during both the encoding and retrieval phases. However, within the Encoding group, MDMA attenuated the recollection of salient details for both positive and negative pictures but had little to no effect on neutral stimuli or familiarity estimates.

5.3. Empathy

Three studies investigating the impact of MDMA on empathy yielded mostly congruent results. Hyseck et al. (2014) and Schmid et al. (2014) reported an overall increase in explicit and implicit emotional empathy, suggesting that MDMA may enhance individuals' ability to understand and share the emotions of others. This increase in emotional empathy was more evident for positive emotional stimuli, according to Schmid et al. (2014). As in Schmid et al. (2014), Kuypers et al. (2014) found an enhancement of emotional empathy but no effect on cognitive empathy, indicating that MDMA might selectively affect

emotional aspects of empathy without altering cognitive empathy or theory of mind. Interestingly, emotional empathy was affected differently in males and females (Hyseck et al., 2014), more specifically, MDMA enhanced ratings of implicit and explicit emotional empathy only in men and not in women.

5.4. Prosocial Behavior

Prosocial behavior encompasses various aspects such as trust, cooperation, generosity, responses to social interactions, moral judgment, and theory of mind. The impact of MDMA on these social cognitive components varied across studies. Some studies reported no significant changes in task-based trust or cooperative behavior following MDMA administration (Borissova et al., 2021; Doss et al., 2018), suggesting that the drug may not consistently affect these aspects of social interaction. Kuypers et al. (2014) analysis of MDMA's main effects on social interaction showed no significant effects on reciprocity or trust in the treatment condition.

In contrast, Gabay et al. (2019) observed specific prosocial effects of MDMA, such as increased cooperative behavior with trustworthy opponents but no effect on cooperation with untrustworthy opponents. This result indicates that MDMA's influence on cooperation may be context-specific, emphasizing the importance of trust in mediating its effects. Concerning altruistic behavior, the Gabay et al. (2018) experiment revealed important results, showing that, during treatment conditions, participants reduced rejections of unfair offers in the first-person condition. Importantly, MDMA increased the percentage of offerings when participants proceeded as proposers, thus enhancing prosocial behavior. Additionally, Kirkpatrick et al. (2015) reported increased generosity towards a friend under the higher dose of MDMA, with almost significantly increased generosity towards a stranger at a lower dose. These results suggest that the influence of MDMA on generosity, being an important factor in prosocial behavior, may vary depending on the dose.

Furthermore, Frye et al. (2014) noted that MDMA was associated with a reduction in the perceived intensity of rejection in social interactions, as measured by the percentage of ball tosses received. This suggests that the drug may impact individuals' sensitivity to social exclusion or rejection. Interestingly, in Kuypers et al. (2018), when participants were under the influence of MDMA alone, they exhibited an equal level of arousal in response to both positive and negative sounds, which was distinct from the placebo and combined ketanserin-MDMA conditions. In the latter two conditions, participants were more aroused by negative stimuli, aligning more closely with the placebo group's response. Importantly,

these findings suggest that MDMA can indeed influence emotional processing, impacting how individuals respond to emotional sounds.

In the study by Schmid et al. (2014), it was not observed significant main effects of the low MDMA dose (75 mg), neither on theory of the mind nor moral judgment.

Discussion

This systematic review intended to study the social cognitive effects of MDMA in healthy individuals. A total of 13 articles were found demonstrating MDMA effects on empathy, facial emotional recognition, processing of emotional sounds, emotional memory, altruistic behavior, generosity, cooperation**,** trust, and rejection sensitivity. Overall findings suggest MDMA's prosocial nature, which will be discussed further below, and its implications in couple therapy.

1. Overview of the Social Cognitive Effects of MDMA

The ability to understand and share the emotions of others, known as empathy, is a central component of promoting prosocial behavior (Decety et al., 2016). According to the empathy and altruism hypothesis, empathy is the emotion that propels an altruistic movement (Batson, 2011; Stocks & Lishner, 2018) – empathy can thus mediate altruistic behavior. Empathy can also help the process of establishing trust. Trust and empathy can be said to complement each other as a premise for effective understanding, communication, and healthy relationships. Furthermore, cooperation depends on empathy.

Empathy is categorized into cognitive empathy and emotional empathy. While cognitive empathy comprises the ability to recognize emotional states in others, emotional empathy corresponds to the emotional response to the other person's emotional state (Blair, 2005). Cognitive empathy under the influence of MDMA appears to be decreased especially when it comes to identifying negative facial expressions (Bedi et al., 2010; Kirkpatrick et al., 2014; Schmid et al., 2014), leaving the identification of positive emotions unaffected (Kirkpatrick et al., 2014). This may be reinforced by the slowed capacity to recognize facial angry expressions (Wardle & de Wit., 2014). Yet, the findings of the studies are incongruent. A significant effect on general facial emotion recognition was observed in at least one study (Hyseck et al., 2014), whereas there were outcomes that indicated no impact on cognitive empathy (Schmid et al., 2014; Kuypers et al., 2014). Besides, Schmid et al. (2014) also found no significant effects in relation to the theory of the mind. Specifically, despite being potentially dissociable constructs (Reniers et al., 2011), cognitive empathy and theory of

mind are both required in terms of comprehending emotions. Moreover, good cognitive empathic abilities depend on the same underlying skills that also enable the theory of the mind, but cognitive empathy concerns the attribution of emotions as opposed to epistemic states such as beliefs and intentions (Cerniglia et al., 2019). Following this logic, presumably, if there is no impact on cognitive empathy, there will be no impact on the theory of mind as well.

In relation to implicit and explicit emotional empathy, MDMA seems to enhance it (Hyseck et al., 2014; Schmid et al., 2014), suggesting that MDMA increases the sensitivity of emotional response to the other person's emotional state. Increased altruism, even in the face of unfair offers (Gabay et al., 2018), can be explained by MDMA's impact on interpersonal sensitivity. This may also be reflected in increased generosity when it comes to a close person, such as a friend (Kirkpatrick et al., 2015).

A key prosocial behavior that underlies successful human interactions is cooperation. The influence of MDMA on cooperation has been explored in two studies, respectively Gabay et al. (2019) and Borissova et al. (2021), but both studies reported distinct outcomes. Regarding Borissova et al. (2021), no significant changes were observed in the trust or cooperative behavior tasks. However, in the investigation by Gabay et al. (2019), an increase in cooperative behavior was reported in the case of trustworthy opponents. These findings suggest that MDMA can promote cooperative tendencies, especially in scenarios involving trustworthiness. Empathy can also be involved in this increase in cooperation dynamics.

The perspective of rejection in a social context changes under the effect of MDMA making it less impactful (Frye et al., 2014). In fact, the impact of negative sound stimuli under the effect of MDMA seems to be lessened, causing the agitation response to be the same as with positive stimuli (Kuypers et al., 2018). These results might encourage prosocial behavior.

It is proposed that moral judgments are also closely linked to prosocial judgments and, as such, prosocial actions often take into account prohibitions, laws, and values (Turiel, 2014). However, no significant results were observed regarding this dimension (Schmid et al., 2014). It is interesting to note that this aspect was assessed under a low dose of MDMA (75mg).

In addition, the effects of MDMA on emotional memory were investigated in a study carried out by Doss et al. (2018), which indicates that MDMA may selectively

influence the encoding processes for emotionally charged stimuli. This suggests that MDMA may alter emotional memory representations.

2. Social Cognitive Effects of MDMA & Couple Therapy

This section seeks to clarify the association between the effects of MDMA on social cognition and couple therapy and to take a critical look at it.

A recent and very relevant study in the field of MDMA-assisted couple therapy, the one by Wagner et al. (2021), aims to investigate how and why the underlying neurobiological and neurochemical effects of MDMA can increase relationship satisfaction when applied to couple therapy. To briefly describe the study, six romantic dyads, one of whose partners had PTSD, were given a treatment in which CBT for PTSD was combined with two sessions of psychotherapy with MDMA. There were no control groups. The outcomes were assessed at mid-treatment, post-treatment, and at 3- and 6-month follow-up. Although the trial focuses on couple therapy in the context of PTSD (this may be because there is a greater depth to the field of investigation about PTSD and MDMA), it has significant connections with the social cognitive effects reported by the studies that were selected for this systematic review.

Improvements in the quality of relationship functioning were demonstrated, which were preserved during both follow-up timepoints (Wagner et al., 2021). Namely, an increase in the perception of relational support and a decrease in conflicts, proving that this intervention can be promising for reinforcing positive social interactions and decreasing negative social interactions in relationships (Wagner et al., 2021). For instance, the findings of the study by Kuypers et al. (2018) demonstrate how MDMA decreases the arousal response to negative sounds. This result may be relevant regarding interpersonal communication and conflict resolution, suggesting that, in the case of MDMA-assisted couple therapy, this will allow partners to be more understanding and tolerant in their responses. In the same logic, the fact that Frye et al. (2014) showed that MDMA can reduce the perceived intensity of rejection may also have a significant effect when applied to couple therapy, plausibly leading participants to be less emotionally reactive and more predisposed to conflict resolution. Besides, Wagner et al. (2021) findings resonate with research indicating that MDMA can amplify cooperation in the case of trusted opponents (Gabay et al., 2019) and increase emotional empathy (Hyseck et al., 2014), which may also be related to the fact that the substance decreases the recognition of angry or fearful faces (Bedi et al., 2010; Kirkpatrick et., 2014; Wardle & de Wit., 2014). Overall, these results can be a facilitator of interpersonal communication and thus they can enhance relationship

satisfaction. In fact, one research, conducted by Baggot et al. (2015), revealed that MDMA had a notable influence on the content of speech when compared to placebo. The study unveiled that MDMA increased the use of social and sexual words, covering both positive and negative emotions.

Moreover, it has been shown that MDMA can moderate representations of emotionally charged memories (Doss et al., 2018). This finding points to the easing of individuals' ability to sustain an optimal tolerance window (Feduccia & Mithoefer, 2018), enabling positive and negative emotions to occur without being avoidant or overcharged. This can promote the person's accessibility to issues that are more difficult to address and thus mutual sharing as a couple.

Finally, the relationship quality outcomes in the Wagner et al. (2021) study found that there was an increase in intimacy. This may be related to an increase in emotional empathy (Hyseck et al., 2014; Kuypers et al., 2014; Schmid et al., 2014), which could have an effect of increasing the connection between the couple. Similarly, the study by Gabay et al. (2018), which suggested greater altruism under the effect of MDMA, and that by Kirkpatrick et al. (2015), which showed an increase in generosity towards a friend, may suggest that there is a greater openness to interpersonal giving, which in turn can be seen as a basic effect that applies to couple therapy.

Despite a probable link between the socio-cognitive effects of MDMA and couple therapy, these assumptions require further research and must consider the idiosyncrasies of couples, which include, for example, the level of emotional intelligence of each partner. Emotional intelligence is a basic skill for maintaining healthy relationships, enabling individuals to communicate effectively, empathize with their partners, and resolve conflicts constructively, and should therefore be considered when screening candidates for therapy. In addition, the prosocial effects of MDMA may depend on the previous level of emotional intelligence. Furthermore, the study by Wagner et al. (2021) has several limitations that make its results not very robust, namely the lack of control groups and the fact that there is no control of confounding variables, such as the effect of the therapeutic intervention.

3. Limitations of the Reviewed Studies

Despite efforts to obtain a valuable sample of articles in the study of the social cognitive effects of MDMA, some limitations were found. Among them, sample sizes vary greatly (between 20 and 65 participants), making it hard to compare results. Also, the selection of participants with various previous experiences with MDMA can influence their

reactions to the drug and thus influence the results. The inclusion of poly-drug users can also be an influencing factor, not only because they are not drug-naive (which can interfere with double-blinding), but also because the use of other drugs can have an interaction effect – although the researchers took care to screen the participants for drug use before each experiment. In general, previous experience with MDMA is a relevant factor that shows a huge variability and this diversity in backgrounds and usage patterns may introduce an additional source of variability in the studies outcomes.

In addition, the differences in the proportion of females within the samples underscore the need for careful consideration of potential sex-related factors when interpreting the findings of these studies and their generalizability to broader populations. As in the case of the study of Hyseck et al. (2014), in which empathy seems to have different outcomes in men and women.

Other important limitations concern the methodology of the intervention. Importantly, the number of sessions varies. Regarding the setting in which the studies were conducted, this was mainly laboratory-based or not mentioned at all. There are already several studies that argue that the setting plays a very important role in the effects of substances used in the field of psychedelic-assisted therapy (Golden et al., 2022), and therefore this aspect should be reported in detail. Additionally, the timepoints for assessing socio-cognitive effects varied considerably between studies, as did the tests used to measure the same construct, such as facial emotional recognition. Finally, the results presented were mostly collected after the drug's peak effect, which is between 90 and 120 minutes (Dumont et al., 2009). As such, the effect on the performance of the tasks may be more intense if the task is carried out during the peak of the drug effect. Indeed, the variation in task selection and assessment timing across studies highlights the complexity of investigating MDMA's effects on cognition and social behavior.

Lastly, the doses of MDMA are not consistent, with fixed doses in some studies and varying depending on weight in others. In the case of studies with variable doses, BMI is a fundamental aspect to take into account and this was either not calculated or showed a lot of variability, adding a layer of complexity when considering the potential influence of body composition on the results. It is worth highlighting that the MDMA effects appear to be dose-dependent.

4. Future Research Directions

Based on the studies already conducted with MDMA, the sample in future studies needs to be optimized and more representative, particularly regarding the sex of the participants and their MDMA experience. Future studies also need to better evaluate the role of the setting. It is also suggested that studies use more consistent and comparable interventive protocols, including similar objective tasks and assessment time points. The lack of follow-up in the studies reviewed is notable, so it is important to consider this aspect in prospective experiments. The definition of standard MDMA dosages, which take into account the BMI of the participants, is also crucial to providing more rigor to the studies.

Future directions should equally focus on the application of MDMA-assisted couple therapy in couples with other types of issues, and not only in the case of the presence of a pathology such as PTSD. Couples therapy assisted by MDMA could take advantage of the prosocial effects shown in this review, benefiting communication, intimacy, conflict management, and other factors that contribute to the quality of couples' relationships. To this end, there is a need for studies in the context of couple therapy that analyze the various dimensions of social cognition and monitor the effects of the intervention implemented. In addition, some studies point to the impact of MDMA on sensual experience and sexual arousal (Kennedy et al., 2010; Kostick & Schensul, 2018), but this impact has not yet been properly studied in couple therapy.

It would also be useful to conduct studies comparing the benefits of couple therapy versus MDMA-assisted couple therapy, finding out how many sessions are needed for there to be significant beneficial effects and whether the use of MDMA possibly shortens the duration of the therapeutic process per se.

Conclusion

This systematic review highlighted the scarcity of articles examining the cognitive-social effects of MDMA, denoting the need for more studies in the area and with more rigorous and standardized methods. Despite this, effects were found in areas of social cognition that indicate the facilitation of social behavior and social bonding by this entactogen. Although not yet widely studied in the context of couple therapy, these effects seem to be greatly beneficial to it, particularly in terms of conflict management, strengthening intimacy, and promoting open and honest communication. Future studies are essential to delve deeper into the effects of MDMA on social cognition and its therapeutic power in couples.

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Appendixes

Table 1

Table covering the details of the included studies

Study	Study Design	Setting	*N (n_{female})	*M_{age} (SD)	$M_{education}$ (SD)	*BMI	*$M_{MDMA\ Experience}$ (SD)	MDMA Dosage ($n_{drug\ sessions}$)	Social Cognitive Target	Tasks and Time of Assessment	Main Findings
Bedi et al. (2010)	Randomized, double-blind, placebo-controlled, within-subjects design	"a comfortable laboratory environment"	21 (9)	24.4 (4.9) y	Not described	18.5–30 kg/m^2	15.0 (23.1) times	0.75 mg/kg; 1.5 mg/kg, orally (4)	Emotion Recognition	*FERT *RMET-R or Eyes test *DANVA-2 (65 minutes post-dose)	Reduced recognition of fearful faces under the higher dose. No effect on the accuracy of emotion recognition from facial or vocal cues.
Borissova et al. (2021)	Counterbalanced, double-blind, placebo-controlled, within-subjects design	Laboratory	25 (7)	34.1 (10.6) y	Not described	Not described	Not described. *21 subjects consumed MDMA, ranging between 1-200 times (Median=*	100 mg MDMA-HCl, orally (2)	Trust, Cooperative Behavior	Public Project Game Dictator game Ultimatum game Trust Investment Task (165-195 minutes post-dose)	MDMA did not significantly change task-based trust or cooperative behavior.

										10, IQR= 3-45)
Doss et al. (2018)	Randomized, double-blind, placebo-controlled, within-subjects design	"The study took place at the University of Chicago Medical Center"	60 (30)	24.90 (0.21) y	**MDMA at encoding:** 15.3 (0.09) y **MDMA at retrieval:** 14.85 (0.08) y	**MDMA at Encoding group (*n*=20):** M= 24.37 (SD= 0.16) kg/m^2 **MDMA at Retrieval group (*n*=20):** M= 23.32 (SD= 0.13) kg/m^2	**MDMA at Encoding group (*n*=20):** 15.95 (0.47) times **MDMA at Retrieval group (*n*=20):** 10.98 (0.41) times	1.0 mg/kg, orally (2)	Emotional Memory	*IAPS (90 minutes post-dose)	No effect in the overall memory accuracy. In the Encoding group, MDMA reduced recollection estimates for negative and positive pictures but little to no effect on neutral items or familiarity estimates.

Frye et al. (2014)	Counterbalanced double-blind, placebo-controlled, within-subjects design	Not described	36 (18)	24.6 (4.7) y	15.1 (1.5) y	19-30 kg/m^2	Not described. *25 subjects consumed MDMA between 1-10 times, and 11 subjects between 11-50 times.*	0.75 mg/kg; and 1.5 mg/kg, orally (3)	Social Acceptance, Rejection Sensitivity	*Cyberball (165 minutes post-dose)	Decreased perceived intensity of rejection, measured as the percent of ball tosses participants reported receiving.
Gabay et al. (2018)	Counterbalanced, double-blind, placebo-controlled, cross-over design	Not described	21 (0)	24.8 (3.7) y	Not described	Not described	Not described. *All participants had at least one previous experience.*	100 mg, orally (1)	Altruistic Behavior	*UG (95 minutes post-dose)	Reduced rejection rates of unfair offers in a first-person condition. MDMA increased the percentage offered when participants acted as the proposer.

Gabay et al. (2019)	Counterbalanced, double-blind, placebo-controlled, cross-over design	Not described	20 (0)	24.8 (3.7) y	Not described	Not described	Not described. *All participants had at least one previous experience*.	100 mg, orally (2)	Social Decision-Making, Cooperation, Trust	*PD (95 min post-dose)	Increased cooperative behavior with trustworthy opponents, but not with untrustworthy opponents. Enhanced recovery (of cooperation) from, but not the impact of, breaches in cooperation.
Hysek et al. (2014)	Randomized, double-blind, placebo-controlled, cross-over design	Not described	32 (16)	25 (3.0) y	Not described	Not described	Not described. *Only 10 subjects had experience with MDMA (<5 times).*	125 mg, orally (1)	Empathy, Emotional Recognition	*MET (180 minutes post-dose) FERT (120 minutes post-dose)	Overall increase in explicit and implicit emotional empathy. Overall impairment in the accuracy of emotion recognition compared with placebo. Emotional empathy and emotion recognition were affected differently in males and females.

Kirkpatrick et al. (2014)	Randomized, double-blind, placebo-controlled, within-and-between-subjects design	Laboratory	65 (25)	23.80 (3.9) y	14.6 (1.4) y	18-30 kg/m^2	15.0 (11.2) times	0.75 mg/kg; and 1.5 mg/kg. Both orally (4)	Emotional Recognition	*mFER (60-120 minutes post-dose)	Reduced accuracy in identifying angry and fearful faces. No effect on the identification of happy faces.
Kirkpatrick et al. (2015)	Randomized, double-blind, placebo-controlled, within-subjects design	Laboratory	32 (9)	24.90 (3.7) y	14.8 (1.2) y	18-30 kg/m^2	17.0 (19.3) times	0.5 mg/kg; and 1.0 mg/kg. Both orally (3)	Generosity	*WTT (90 minutes post-dose)	Increased generosity towards a friend, but not towards a stranger under the highest dose. No effect on generosity towards the friend at the lowest dose, but there was an almost significant increase in generosity towards a stranger (p = 0.053).
Kuypers et al. (2014)	Randomized, double-blind, placebo-controlled, within-subjects design	Not described	20 (8)	21.60 (2.45) y	Not described	Not described [*M_{weight}= 70.25 (13.09) kg]	10.95 (8.97) times	75 mg, orally (4)	Empathy, Social Interaction	*RMET and MET (105 minutes post-dose) Trust Game (120 minutes post-dose)	Enhanced emotional empathy. No effect on cognitive empathy. No effect on social interaction measures (i.e., trust & reciprocity).

Kuypers et al. (2018)	Randomized, double-blind, placebo-controlled, within-subjects design	Not described	20 (8)	21.20 (2.6) y	Not described	Not described	16.80 (23.2) times	75 mg, orally (1)	Processing of Emotional Sounds, Implicit Attitudes	*PAST and *AAT (90 min post-dose)	Reduction of arousal in response to negative sounds. No effect on cognitive bias towards emotional or social stimuli.
Schmid et al. (2014)	Randomized, double-blind, placebo-controlled, cross-over design	"a quiet hospital research ward."	30 (15)	24 (4.2) y	Not described	18-27 kg/m^2	Not described. *Only 8 subjects had experience with MDMA (<5 times).*	75 mg, orally (3)	Moral Judgment, *ToM, Empathy, Emotional Recognition	FERT (75 minutes post-dose) MET (90 minutes post-dose) *MJT (120 minutes post-dose) *MASC (180 minutes post-dose)	Increased explicit and implicit emotional empathy for positive emotional stimuli. No effect on cognitive empathy, ToM, behavior, and moral judgment.

Wardle & de Wit (2014)	Counterbalanced, double-blind, placebo-controlled, within-subjects design	'Sessions were conducted (…) in a "living room" style laboratory.'	36 (18)	24.6 (4.7) y	15.1 (1.5) y	19-30 kg/m^2	10.2 (8.2) times	0.75 mg/kg; and 1.5 mg/kg. Both orally (3)	Emotional Perception	*DEIT (between 70-110 minutes post-dose)	Slowed perception of angry expressions under the higher dose.

Note. M_{age}: mean age; SD: standard deviation; N: sample size; BMI: Body Mass Index; M_{MDMA} experience: mean MDMA experience; M_{weight}: mean weight; FERT: Face Emotion Recognition Task; RMET-R or Eyes test: Reading the Mind in the Eyes – Revised test; DANVA-2: Diagnostic Analysis of Nonverbal Behavior - Second Edition; IAPS: International Affective Picture Set; Cyberball: Cyberball games; UG: The Ultimatum Game; PD: The Prisoner's Dilemma; MET: Multifaceted Empathy Test; RMET: Reading the Mind in the Eyes Test; PAST: The Processing of Affective Sounds Task; AAT: Approach-Avoidance Task; mFER: Morphed Facial Expression Task; WTT: Welfare Trade-Off Task; MJT: Moral Judgment Task; MASC: Movie for the Assessment of Social Cognition; ToM: Theory of Mind; DEIT: Dynamic Emotional Identification Task.

Table 2

Overview of the number of sessions involving MDMA, placebo, and other substances across the reviewed studies

Authors (Year)	MDMA ($n_{sessions}$)	Placebo ($n_{sessions}$)	Other substances ($n_{sessions}$)
Bedi et al. (2010)	4	4	4 (Methamphetamine)
Borissova et al. (2021)	2	2	-
Doss et al. (2018)	1	1	-
Frye et al. (2014)	3	3	-
Gabay et al. (2018)	1	1	-
Gabay et al. (2019)	1	1	-
Hysek et al. (2014)	1 (Cross-over)	1 (Cross-over)	-
Kirkpatrick et al. (2014)	4	4	4 (Oxytocin)
Kirkpatrick et al. (2015)	2	1	1 (Placebo)

Kuypers et al. (2014)	4	4	4 (Pindolol, Oxytocin)
Kuypers et al. (2018)	1	1	-
Schmid et al. (2014)	1 (Cross-over)	1 (Cross-over)	1 (Methylphenidate)
Wardle & de Wit (2014)	3	3	-