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Title: A Meta-Analysis of Craving Studies in Schizophrenia Spectrum

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A Meta-Analysis of Craving Studies in Schizophrenia Spectrum Disorders

Objective: DSM-5 Substance Use Disorders (SUD) are frequent and debilitating comorbidities displayed by patients with schizophrenia spectrum disorders (SZ). One crucial feature of SUD is drug craving, an intense desire to consume a substance, commonly divided into reward and relief dimensions. Here, we conducted a meta-analysis of studies investigating craving in individuals with both SUD and SZ in order to examine whether these patients exhibit a distinct pattern of craving as compared to patients with SUD without SZ.

Method: Meta-analysis based on the PRISMA guidelines.

Results: Sixteen relevant publications were identified by a systematic search of databases, which included 1219 individuals (589 SUD-SZ and 630 SUD-without-SZ). Of the 16 studies, 11 focused on tobacco, 3 on cannabis and 2 on cocaine. When considered across all studies, SUD-SZ had significantly higher scores than SUD-without-SZ for global craving with medium effect size ($k_{\text{number of studies}}=16$, $Zr=0.20$ [0.15, 0.26], equivalent $d=0.41$, $p<.001$). Discrete patterns emerged for reward ($k=7$, $Zr= 0.10$ [0.02, 0.17], equivalent $d= 0.20$, $p<.05$) and relief ($k=7$, $Zr= 0.25$ [0.17, 0.33], $d= 0.52$, $P<.001$) craving, and the direct comparison revealed a significantly greater effect for relief than reward ($\chi^2(1)=7.40$ $p=.007$).

Conclusion: These results suggest that SUD-SZ cases experience higher craving, more specifically for relief, in comparison to patients with SUD-without-SZ. These clinical findings can foster the development of tailored addiction therapies for this specific comorbid population.

KEY-WORDS: Schizophrenia; Substance Use Disorder; Addiction; Craving; Meta-analysis

1. INTRODUCTION

Patients with schizophrenia spectrum disorder (SZ) frequently present with comorbid substance use disorders (SUD). Whatever the substance use disorder, prevalence rates of SUD in SZ lies at around 50% of patients (e.g. ~70% comorbidity with tobacco (Cooper et al., 2012), ~40% with cannabis (Rathbone et al., 2008)) and reaching up to 50% with cocaine (Mohite et al., 2015)), which is significantly higher than in the general population (approximately 10% lifetime across all substances (Grant et al., 2016)). Furthermore, SUD in SZ are associated with poorer clinical outcomes and increased morbi-mortality (De Witte et al., 2014; Volkow, 2009) even at early stages of the illness (Oluwoye et al., 2018). Therefore, a better understanding of the clinical features of SUD in psychosis is crucial to improve comorbid patients' treatment and prognosis.

Several hypotheses have been proposed to explain the high comorbidity between SZ and SUD. One of them, the "self-medication hypothesis", considers SUD as secondary to the psychiatric disorder manifestations or to medication side effects. For instance, this hypothesis states that SZ patients use drugs to relieve their psychiatric symptoms and cognitive deficits, and to attenuate antipsychotics' side effects (Khantzian, 1997; Kumari and Postma, 2005). On the other hand, the more recent "primary addiction" (or "shared vulnerability") hypothesis proposes that shared genetic/environmental risk factors and neurobiological dysfunctions inherent to the pathophysiology of SZ make these subjects more vulnerable to substance consumption but does not induce a "volitional" act of use for self-help, thereby challenging the self-medication hypothesis (Boggs et al., 2018; Hahn et al., 2013; Sagud et al., 2018). A unifying hypothesis proposes that the genetic determinants of risk for SZ make patients vulnerable to substance abuse which, in turn, serves as an additional risk factor for the appearance of SZ symptoms (Khokhar et al., 2018).

More specifically, the primary addiction model suggests that SZ and SUD are the expression of common mechanistic abnormalities within the meso-cortico-limbic dopamine system (Chambers et al., 2001). Indeed, this system is thought to mediate the rewarding effects of drugs, specifically via dopamine neurons in the ventral tegmental area and their target neurons in the ventral striatum and the prefrontal cortex. Thus, alterations within these mechanisms might be implicated in pathological motivational states (i.e. excessive drug wanting) in patients with SUD (Koob and Volkow, 2010; Volkow and Morales, 2015). ~~Crucially~~ In parallel, the implication of the meso-cortico-limbic dopamine system is one of the most robust findings regarding the pathophysiology of SZ (Brunelin et al., 2013). Most results converge toward an early dysregulation in the striatum, especially in the rostral caudate, manifesting as excess dopamine synthesis and release. In addition, the deficit has been shown to extend to other extrastriatal subcortical regions and most cortical areas (Weinstein et al., 2017). Thus, these abnormalities in the meso-cortico-limbic dopamine system may make these patients more vulnerable to the rewarding effects of substances and increase risk to develop SUD (Khokhar et al., 2018).

Interestingly, the meso-cortico-limbic dopamine system seems also involved in mediating drug craving, one central feature of SUD (Robinson and Berridge, 1993; Sinha, 2013). Craving is typically defined as an intense desire to consume a substance. It has been emphasized that craving has considerable utility for diagnosis and as a clinical outcome (Tiffany and Wray, 2012). Furthermore, craving has recently been introduced as a diagnostic criterion for SUD in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force., 2013). While the clinical significance of craving is still under debate, it has been considered as a relevant treatment target and outcome measure for SUD therapies. For instance, some cognitive-behavioral therapies for SUD specifically focus on reducing craving

(Potenza et al., 2011). However, psychosocial interventions appear less efficient for SUD in patients with SZ. A better understanding of craving would provide fruitful result to refine these interventions in comorbid populations (Hunt et al., 2019).

Craving has been extensively investigated as a metric associated with SUD. It can be measured at baseline, which is a steady state of craving without experimental procedure. Experimentally, it can be assessed in the context of specific manipulations, such as transient abstinence, stress induction, exposure to drug-related cues (e.g., drug pictures or videos) and imaginal exposure (e.g., imagining a scenario involving drug use). Moreover, various psychometric tools have been used to measure craving such as standardized multi-item questionnaires or single-item ratings. Finally, craving has been approached as a multivariate construct with at least two subtypes: reward craving – desire for the rewarding effects of drugs, and relief craving – desire for the reduction of negative affective state or withdrawal (Cox et al., 2001; Glockner-Rist et al., 2013; Heinz et al., 2003; Verheul et al., 1999).

However, to date, only a few studies have investigated craving in participants with SZ. Some results indicate significantly higher craving intensity in SZ participants with SUD (SUD-SZ) as compared to participants with SUD-without-SZ (e.g. (Esterlis et al., 2014; Potvin et al., 2016), while others did not (Smelson et al., 2002; Weinberger et al., 2007). Given the crucial role of craving in SUD and the high comorbidity between SUD and SZ, it seems important to better investigate and characterize craving in patients with SZ.

Here, we present a meta-analysis of studies investigating craving in participants with SZ in order to examine whether patients with both disorders (SUD-SZ) exhibit a specific pattern of craving as compared to patients with SUD-without-SZ. A large body of evidence shows that SZ is associated with severe dysfunctions of the brain reward circuitry. In parallel, the “self-medication” hypothesis indexed by relief-seeking suggests a higher sensitivity to reward that relief in patients with SZ. Therefore, we hypothesized that participants with SUD-

SZ would display higher overall (global) craving intensity, but we also expected that the group differences would be more pronounced for relief craving than reward craving. As a secondary objective, we aimed to examine the effect of the experimental condition (baseline, substance privation-induced withdrawal, or drug-cue exposure) and the effect of the type of substance on the observed effect sizes. With the aim of pooling the most comparable and consensual results, we chose to account only for substances that are listed in DSM 5 descriptions for SUD. We believe that a better understanding of craving in patients with SZ could contribute to the development of better-targeted approaches to treat SUD in this specific population.

2. METHOD

2.1. Search strategy and selection criteria

A systematic review and meta-analysis was conducted following the Cochrane group recommendations (Chandler, 2011) and PRISMA guidelines (Moher et al., 2009).

2.1.1. Eligibility

The criteria for inclusion were: i) articles published in English in peer-reviewed journals; ii) studies comparing participants with SUD-SZ (schizophrenia, schizo-affective disorder, schizophreniform disorder, psychotic disorder not otherwise specified) with participants with SUD-without-SZ; iii) studies including participants with an established clinical diagnosis of SUD accounting for substances listed in DSM 5, i.e., amphetamines, alcohol, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine, SHA (sedative,

hypnotics, and anxiolytics), stimulants and tobacco (American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force., 2013); iv) studies including participants with an established clinical diagnosis of schizophrenia spectrum disorder according to DSM; v) studies reporting sufficient data (self-reported craving) to calculate the effect size of the craving difference between groups; vi) clear information regarding the conditions in which craving was assessed (baseline craving, drug-cue exposure and/or substance privation-induced withdrawal).

2.1.2. Search strategy

We first searched the PubMed and Embase databases using the following terms with no publication date restrictions: (“Schizophrenia”[Mesh] OR Schizophreni*[Text Word]) AND (“Craving”[Mesh] OR Craving*[Text Word] OR Urge[Text Word]). The “similar articles” function in PubMed and reference lists in identified studies were also reviewed. Additional references were then gathered using a combination of the above mentioned text words in the Embase database. Two authors (CD, FH) independently screened the title, abstract, and keywords of each study identified by our search strategy to determine if they met the inclusion criteria. Then, the same procedure was applied to the full text of eligible studies. Authors were contacted to provide missing data. Discrepancies between reviewers were resolved by discussion with a third reviewer. The literature search strategy and results of the eligibility assessment are detailed in Figure 1.

2.2. Data extraction

Two of the authors (CD, FH) independently extracted the following data, when available: i) sample size; ii) demographic data: mean age, gender ratio, ethnicity, average level of education; iii) clinical features: diagnoses, SUD duration, severity of SZ symptoms

measured by the Positive And Negative Syndrome Scale – PANSS (Kay SR, 1987), concomitant antipsychotic treatments; iv) craving measures scores with type of craving (global – undifferentiated, reward, relief), type of experimental condition (baseline, withdrawal, drug-cue exposure) and type of substance. When this information was not reported, authors were contacted.

2.3. Meta-analysis

This meta-analysis was based on the procedures proposed by Rosenthal (Rosenthal, 1991; Rosnow, 2003), based on the effect size r (ES r) as the measure of effect sizes. ES r can be readily converted into the well-known Cohen's d (Rosenthal, 2001), but ES r offers the advantage of being more flexible, as it can be calculated for instance from non-parametric statistics, which are often used for behavioral scales. For this meta-analysis, ES r of the difference between participants with SUD-SZ and participants with SUD-without-SZ was calculated for each craving measure of each study, such that positive values indicated greater craving in the SUD-SZ group and negative values indicated greater craving the SUD-without-SZ group. A Fisher transformation was then applied to transform the ES r of each study into a Zr (standardized ES r), which is required for further analyses. Zr can be interpreted as follows: $Zr \leq .10$ can be considered a small effect, a Zr between .10 and .50 can be considered as a medium effect and a $Zr \geq .50$ as a large effect (33).

While the distinction of reward and relief craving was an important focus of this meta-analysis, some studies included only a global score (see results section). Hence, to combine all studies we first focused on the global craving scores, for which we computed a weighted-mean Zr s (taking sample size into account). Some studies provided data for reward and relief scores and not for global scores, but in these cases a global craving Zr could nonetheless be obtained by averaging the Zr s of the reward and relief scores.

Next, weighted-mean Z_r s were computed for the studies reporting reward craving scores and relief craving scores, and compared with each other using focused tests (Rosenthal, 1991; Rosnow, 2003) in order to determine if the group differences are greater for one type of craving.

Finally, focused tests were also used to examine the effect of the condition and the effect of the type of substance on the magnitude of the Z_r s, which was first done for the global craving scores, and also for the reward and relief craving scores.

2.3.3 Publication bias and fail-safe N

We examined the possibility of a publication bias by visual exploration of the funnel plot and calculated a Rosenthal's fail-safe N (Orwin, 1983; Rosenthal, 1979), in both cases focusing on the global craving scores that were available for all the studies included in the meta-analysis. The fail-safe calculation was suggested to explore if some statistically non-significant studies missing from an analysis would reduce the observed effect to a level not statistically significantly different from zero if included. To this end, Rosenthal's method calculates the "fail-safe" number of additional studies "N" with mean null result necessary to reduce the combined significance to a p -value = 0.05 (McDaniel, 2006). In other words, the fail-safe N is the number of missing studies averaging a z -value of zero that should be added to make the Z_r (standardized ES_r) statistically non-significant.

For all statistical analyses, the α level for significance was set at $P < 0.05$.

3. RESULTS

3.1. Studies retained in the meta-analysis

Overall, 16 studies were eligible for meta-analysis (Ahnallen and Tidey, 2011; Carol et al., 2001; Dekker et al., 2010; Esterlis et al., 2014; Freeman et al., 2014; Kuepper et al., 2013; Lo et al., 2011; Potvin et al., 2016; Schnell T, 2013; Smelson et al., 2002; Tidey et al., 2014; Tidey et al., 2005; Tidey et al., 2008; Tidey et al., 2013; Weinberger et al., 2007; Williams et al., 2011) including a total of 1219 individuals: 589 participants with SUD-SZ and 630 participants with SUD-without-SZ. Figure 1 presents the flowchart leading to the inclusion of the 16 eligible studies and Table 1 presents the characteristics for each of these 16 studies.

* PLEASE INSERT FIGURE 1 ABOUT HERE *

3.2. Tools used to assess craving in the included studies

All 16 studies included in this meta-analysis relied on craving rating-scales that measured global craving, and some studies relied on tools that further distinguished the specific dimensions of reward and relief craving. The measures allowing this distinction between reward and relief craving included the Questionnaire for Smoking Urge (QSU), the QSU brief version, the Tobacco Craving Questionnaire (TCQ) and the German Cannabis-Craving Scale (CCS-7).

Of the 16 studies, 11 investigated tobacco craving, 3 investigated cannabis craving and 2 investigated cocaine craving. For the assessment of tobacco craving, 6 studies (Esterlis et al., 2014; Tidey et al., 2014; Tidey et al., 2008; Tidey et al., 2013; Weinberger et al., 2007; Williams et al., 2011) assessed participants with the QSU (Cox et al., 2001) and 2 studies

(Freeman et al., 2014; Lo et al., 2011) used the Tobacco Craving Questionnaire (TCQ), either its short form (Heishman et al., 2008) or the full French version (Berlin et al., 2010). The other 3 studies focusing on tobacco craving used a visual analog scale for current urge to smoke (Ahnallen and Tidey, 2011; Freeman et al., 2014; Tidey et al., 2005). For cannabis craving, one study (Schnell T, 2013) used a German Cannabis-Craving Scale (CCS-7) (Schnell T, 2011), whereas the other two studies (Dekker et al., 2010; Kuepper et al., 2013) used the Obsessive Compulsive Drug Use Scale (OCDUS) (Franken, 2003) that targets only global craving. In both cocaine-craving studies included in the meta-analyses (Carol et al., 2001; Smelson et al., 2002), craving for cocaine was assessed with the Voris Cocaine Craving Scale (VCCS) (Smelson et al., 1999), a tool that only targets global craving.

* PLEASE INSERT TABLE 1 ABOUT HERE *

3.3. Quantitative synthesis (meta-analysis, Table 2)

3.3.1. Global craving differences

For global craving, examined across conditions and types of substances, the weighted mean effect size of the group difference (SUD-SZ versus SUD-without-SZ) across all 16 studies was of $Z_r=0.20$ (Confidence Interval [0.15, 0.26], equivalent $d=0.41$, $p<.001$), with the positive value of the Z_r indicating that the SUD-SZ group presented higher craving scores than SUD-without-SZ. The fail-safe N was of 233, which means that 233 studies should be added to make this weighted-mean Z_r statistically non-significant. This constitutes an unlikely number of unpublished or unretrieved studies with inconclusive results. A visual exploration of the funnel plot revealed no publication bias (see supplementary material S1). Significant

heterogeneity was however observed between the effect sizes of the different studies included in the meta-analysis ($\chi^2(15) = 32.27, p = .006$).

3.3.2. Reward versus relief craving

The comparison of the effect sizes obtained for reward and relief revealed a significant effect ($\chi^2(1) = 7.40, p = .007$), such that the groups differed to a lesser extent for reward ($Z_r = 0.10, k_{\text{number of studies}} = 7$) and to a greater extent for relief (mean weighted $Z_r = 0.25, k = 7$). Significant heterogeneity was detected between the studies focusing on reward craving ($\chi^2(7) = 45.01, p < .001$) whereas the studies focusing on relief showed no significant heterogeneity ($\chi^2(5) = 7.93, p = .16$).

3.3.3. Effect of condition

When assessing the effect of condition for global craving scores, a significant effect of condition emerged ($\chi^2(1) = 13.42, p = .001$), with a mean weighted $Z_r = 0.15$ for baseline craving ($k = 13$), a mean weighted $Z_r = 0.11$ for withdrawal ($k = 3$) and a mean weighted $Z_r = 0.41$ for drug cue ($k = 5$). Significant heterogeneity was identified between studies targeting baseline craving ($\chi^2(12) = 43.04, p < .001$) and drug cue ($\chi^2(4) = 14.31, p < .006$), but not between studies focusing on withdrawal ($\chi^2(2) = 2.39, p = .30$). Paired comparisons revealed no significant difference between baseline and withdrawal ($\chi^2(1) = 0.22, p = .63$), while the drug cue condition differed significantly from both baseline ($\chi^2(1) = 12.45, p = .0004$) and withdrawal ($\chi^2(1) = 7.70, p = .005$).

When assessing the effect of condition for the reward craving scores, only the baseline and withdrawal conditions could be examined, as there was no study for drug cue. The mean weighted effect size for baseline reward craving was $Z_r = 0.08$ ($k = 6$), with significant heterogeneity between the studies ($\chi^2(5) = 45.54, p < 0.001$). The mean weighted effect size

for withdrawal reward craving was $Z_r = 0.21$ ($k=3$), also with significant heterogeneity between the studies ($\chi^2(2) = 6.51, p=.04$). No significant difference emerged between the effect sizes of these two conditions ($\chi^2(1) = 2.05, p=.15$).

When assessing the effect of condition for relief craving scores specifically, here again only the baseline and withdrawal conditions could be examined as there was no studies for drug cue. The mean weighted effect size for baseline relief craving was $Z_r = 0.30$ ($k=6$), with significant heterogeneity between the studies ($\chi^2(5) = 25.78, p<.001$). The mean weighted effect size for withdrawal relief craving was $Z_r = 0.31$ ($k=3$), without significant heterogeneity between the studies ($\chi^2(2) = 1.43, p=.49$). No significant difference emerged between the effect sizes of these two conditions ($\chi^2(1) = 0.008, p=.93$).

Overall, there was no evidence for differences in effect sizes between the baseline and withdrawal conditions, but the drug cue condition examined only on global craving measures showed a larger effect size of the between group difference.

3.3.4. Effect of substance

When comparing the effect sizes obtained for studies focusing on the different substances (tobacco, cannabis and cocaine), no significant difference in effect sizes emerged when considering the global craving scores ($\chi^2(2) = 0.15, p=.92$). The weighted mean Z_r s for tobacco, cannabis and cocaine were respectively of 0.20 ($k=11$), 0.18 ($k=3$) and 0.23 ($k=2$), with significant heterogeneity between studies targeting tobacco ($\chi^2(10) = 23.34, p=.009$) and cannabis ($\chi^2(2) = 7.64, p=.02$), but not those targeting cocaine ($\chi^2(1) = 1.13, p=.28$).

When looking at the effect of substance for the reward craving scores specifically, the single study targeting cannabis showed a negative effect size of $Z_r = -0.26$ (i.e. lesser reward craving in SUD-SZ versus SUD-without-SZ), which significantly differed from the mean

weighted effect size of the studies targeting tobacco ($Z_r = 0.16$, $k=7$, effect of substance: $\chi^2(1) = 15.07$, $p < .001$).

When looking at the effect of substance for the relief craving scores specifically, the single study targeting cannabis had a $Z_r = 0.33$, which did not significantly differ from the studies targeting tobacco (mean weighted $Z_r = 0.23$, $k=5$, effect of substance: $\chi^2(1) = 1.23$, $p = .29$).

* PLEASE INSERT TABLE 2 ABOUT HERE *

4. DISCUSSION

To the best of our knowledge, this is the first meta-analysis that compared craving between participants with SUD-SZ versus participants with SUD-without-SZ.

4.1. SUD-SZ cases experience higher craving, more specifically for relief

In line with our hypothesis, the main result shows a significant medium effect size indicating higher global craving in participants with SUD-SZ compared to participants with SUD-without-SZ when all experimental conditions and substances are factored together. Moreover, the comparison of effect sizes showed that the difference between SUD-SZ and SUD-without-SZ participants was significantly higher for the relief dimension than the reward dimension. Though these results support both a higher sensitivity to reward-seeking and the “self-medication” hypothesis (Khantzian, 1997; Kumari and Postma, 2005) indexed by relief-seeking, data lead us to advocate a prominence of the latter. Indeed, the urge for consuming substances seems more explained by the desire to decrease a negative affective state than by reward-seeking in patients with SZ. Our results thus suggest a consumption of substances aimed to cope with symptoms and/or medication side effects as a plausible

explanation in patients with schizophrenia (Awad and Voruganti, 2015). These findings also concur with a study reporting higher levels of negative affect and lower ability to cope in patients with SZ (Steinberg et al., 2010), as well as lower level of positive affect, which may result in greater anticipation that smoking will relieve negative affect compared to controls. These assumptions are supported by studies reporting a reduction of negative affect as the most important motive for drug use in participants with SUD-SZ (Ahnallen and Tidey, 2011; Dixon et al., 1990; Tidey and Rohsenow, 2009). Another reason for an increase relief-oriented craving in patients with SZ could rely on the fact that abstinence disrupts working memory performance in these people and that resumption of smoking reverses this deficit (Evins et al., 2005; Sacco et al., 2005). Nevertheless, the data included in our analysis do not permit us to identify which symptoms are targeted by substances in participants.

Despite our results support the “self-medication” hypothesis, it is noteworthy that more recent publications erode the emphasis on this model to understand high rates of SUD in SZ (Boggs et al., 2018; Hahn et al., 2013; Manzella et al., 2015; Sagud et al., 2018). Several studies included in our meta-analysis demonstrate high levels of craving in both participants with SUD-SZ and SZ. In line with the primary addiction model, we can speculate that craving proneness is also an expression of common physiopathological mechanisms of these disorders.

4.2. Effects of experimental condition and substance on craving patterns

When considering the drug-cue condition, the mean weighted effect size available for global craving differed significantly from the effect sizes observed in baseline and withdrawal conditions. This is consistent with the increased sensitivity to drug-associated cue in SZ participants, which has been related to an hyperactivity of the meso-cortico-limbic dopaminergic system (Chambers et al., 2001). By contrast, no significant differences were

observed between baseline and withdrawal conditions, be it for global craving or when assessed separately for reward and relief craving. This suggests that while patients with SUD-SZ experience higher craving at baseline than SUD-without-SZ, that effect is not significantly increased by the privation of substance across the included study.

In parallel, when comparing the effect sizes obtained for studies focusing on the different substances (tobacco, cannabis and cocaine), no significant difference emerged when considering the global and relief craving scores. However, when considering reward craving only, the single study targeting cannabis showed a negative effect size (i.e., indicating greater reward craving in the SUD-without-SZ group), which significantly differed from the mean weighted effect size of the studies targeting tobacco. This suggests that people without schizophrenia (SUD-without-SZ group) are more likely to use cannabis for reward or pleasure (i.e. recreationally) while people with schizophrenia may be less affected by the rewarding aspect of cannabis use. Three studies assessing craving experiences for substances that are not listed in SUD disorder (Food (Abbas and Liddle, 2013; Lungu et al., 2013) and Caffeine (Adolfo et al., 2009)), not included in our meta-analysis) reported higher global craving measures in participants with SUD-SZ, though these studies did not distinguish between reward and relief craving. Taken together, these results and those of the current meta-analysis support that craving proneness in patients with SZ goes both across and beyond DSM 5 SUD categories.

4.3. Strengths and limitations

The strengths of the current study are the large sample of subjects, and that identified studies emanated from different groups of researchers. However, several limitations should be acknowledged. First, almost all heterogeneity tests between effect sizes were significant, likely as a result of methodological differences across studies (e.g. different craving scales,

drug-cue types, withdrawal durations). Moreover, several heterogeneity χ^2 that were non-significant were based upon analysis of a few studies ($N < 5$), which provide little power to reject the null hypothesis of homogeneity even if significant heterogeneity is present (Hardy and Thompson, 1998). Second, the use of craving measures at baseline may have biased craving scores. Indeed, craving is responsive to drug-related stimuli and can be lowered by the absence of substance or drug-related stimuli (Smelson et al., 2002). In addition, at the time of the ratings, one subject may recall a situation involving high craving while another subject may recall a situation with lower craving. Furthermore, such recall effects may be vulnerable to cognitive distortions (Robbins et al., 2008), and the memory deficits often reported in schizophrenia (Fioravanti et al., 2012) could also impact their judgments. Third, another limitation is that most of the studies included in the meta-analysis investigated craving for tobacco (11 among 16 included studies). This could be a limitation for the implications of our finding for non-tobacco SUD. Fourth, reports of variables known to have a significant effect on drug use (e.g., ethnicity, education, migration status (Gerra et al., 2020; McCabe et al., 2007; Rolland et al., 2017)) were inconsistent across studies. This prevented us to conduct statistical analyses exploring the influence of these potential biases on craving differences. Finally, in the current meta-analysis, we investigated craving differences between SUD-SZ and SUD-without-SZ but other outcomes related to substance consumption would also be worthy of investigation since the intensity of craving do not always correlate with increased substance consumption (Donny et al., 2008).

4.4. Therapeutic prospects

Although specific interventions for comorbid populations (SZ-SUD) are few, psychological approaches to tackle substance use are thought to be effective in SZ patients, according to a recent review (De Witte et al., 2014). The current meta-analysis provides

further insights to better tailor the treatments for comorbid populations. More specifically, our results suggest that current non-pharmacological approaches targeting SUD should focus specifically on the relief dimension of craving. Therefore, dysfunctional cognitions on relief effects of substance should be targeted by psychoeducational approaches, as these cognitions are an important mediator in the continuation of substance use and craving (Dekker et al., 2010). As a prevention strategy, urge for substances should be assessed in patients with SZ with specific rating-scales, as craving worsening may be missed when relying only on assessments such as the Fagerström Test for Nicotine Dependence (Steinberg et al., 2005).

5. CONCLUSION

To conclude, drug craving must be considered as a major clinical dimension of comorbid SUD in patients with SZ, especially regarding relief-oriented craving. Moreover, this craving dimension should be highlighted as a relevant therapeutic target in comorbid populations, with the twofold aim of reducing substance use and preventing drug-related morbidity. The specificity of craving patterns could inform motivational interviewing strategies and psychoeducational contents. Further studies are required to address craving more extensively among substances.

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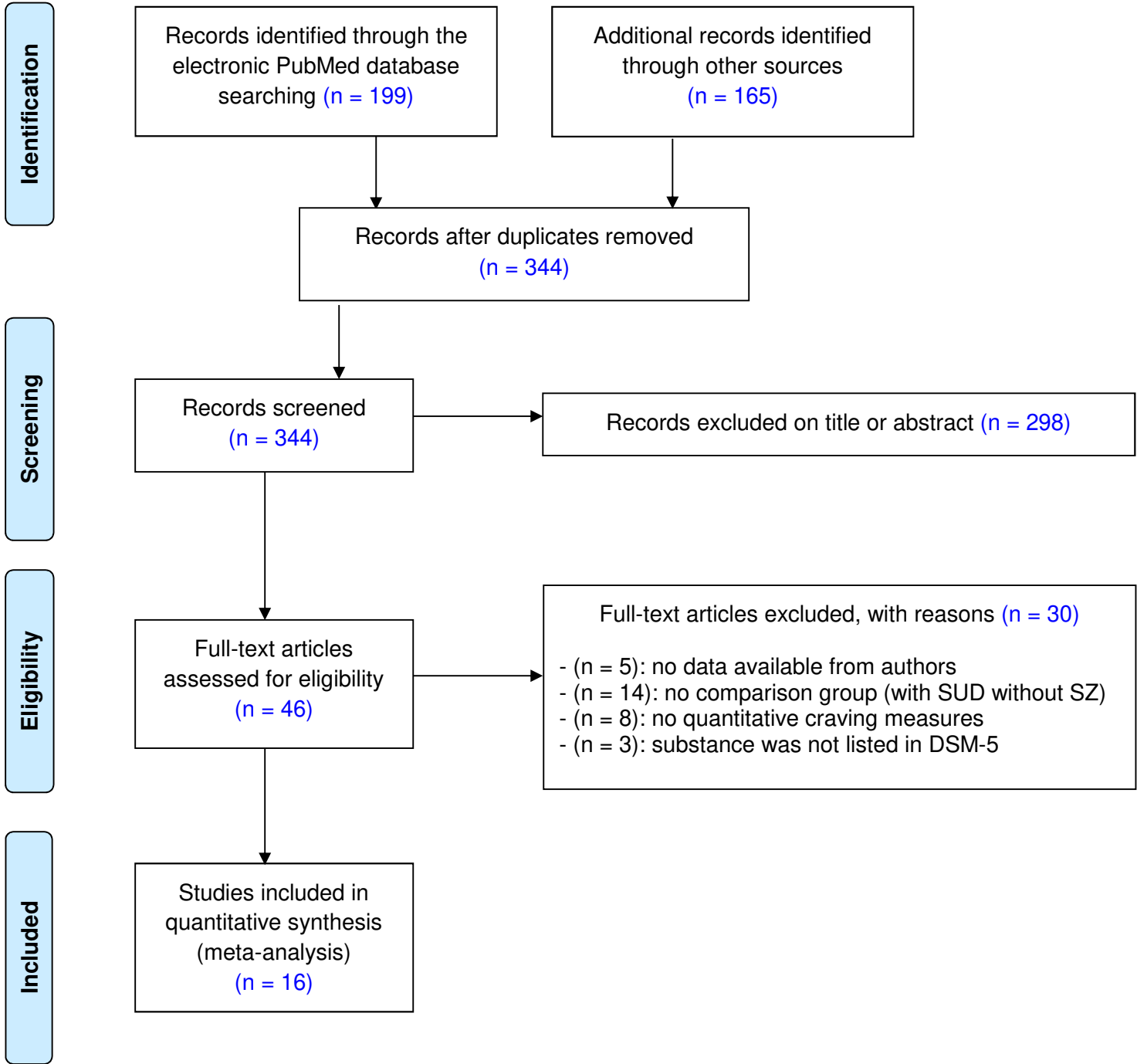
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FIGURES LEGENDS

Figure 1: Flow diagram for the systematic review and meta-analysis.

Pubmed electronic database were searched using the following headings: **(Schizophrenia[Mesh] OR Schizophreni*) AND (Craving[Mesh] OR Craving* OR Urge)**. Additional references were gathered using a combination of the above mentioned text words in Embase database.



Study				Patients with SUD-SZ											Craving measures			
Author and year	SZ sample diagnosis	N SUD-SZ	N SUD-without-SZ	Age	Female (%)	Ethnicity	Educ (years)	PANSS total	PANSS +	PANSS -	PANSS general	Treatment (CPZ)	SUD duration	Consumption		Scale	Dimension & condition	Effect size (Zr)
														Cig/day	FTND			
Tobacco																		
AhnAllen & Tidey, 2010	SZ/SZA	10	10	44.5	20%	W: 80% B: 10% NA:10%	10.8	43.2	10.4	10.5	22.3	-	-	30.1	7.6	Urge VAS	G – baseline G – cue exposure	0.10 0.01
Esterlis et al., 2014	SZ	22	22	42.1	9%	-	-	73.0	19.2	35.0	18.8	-	25.6	20.7	5.7	QSU	G – baseline G – withdrawal Rw – baseline Rw – withdrawal Re – baseline Re – withdrawal	0.11 0.29* 0.05 0.35* 0.28* 0.43*
Freeman et al., 2013	SZ	22	23	38.1	36%	-	-	43.2	13.4	9.6	-	413.6	19.7	19.4	6.1	Urge VAS	G – baseline G – cue exposure	0.48* 0.56*
Lo et al., 2011	SZ/SZA	100	100	43.3	29%	W: 61% B: 37%	12	-	-	-	-	-	27.1	30.4	5.5	TCQ	G – baseline Rw – baseline Re – baseline	0.29* 0.15* 0.32*
Potvin et al., 2016	SZ/SZA	18	24	34.8	22%	W: 77% B: 23%	11.4	-	15.4	15.4	-	579.1	19.1	18.8	6.2	TCQ	G – baseline G – cue exposure	0.25 0.15*
Tidey et al., 2013a	SZ	28	27	44.0	43%	W: 69% B: 19% H: 7%	11.4	60.0	-	-	-	-	24.9	21.6	6.3	QSU-brief	G – withdrawal Rw – withdrawal Re – withdrawal	0.08 -0.07 0.22
Tidey et al., 2013b	SZ	30	26	46.2	40%	W: 77% B: 10% H: 10%	11.9	52.1	11.6	14.6	25.9	-	27.4	25.9	6.4	QSU-brief	Rw – baseline Rw – withdrawal Re – baseline Re – withdrawal	0.82* 0.37* 0.87* 0.28*
Tidey et al., 2008	SZ/SZA	21	21	44.1	33%	W: 57% B: 13% H: 4%	-	68.6	16.7	18.3	33.6	-	26.4	32.6	7.7	QSU-brief	G – baseline G – withdrawal	0.18 -0.04
Tidey et al., 2005	SZ/SZA	20	20	47.0	35%	W: 45% B: 15% H: 10% NA: 20%	-	70.7	17.2	19.1	34.4	-	28.0	25.9	6.9	Urge VAS	G – cue exposure	0.13
Williams et al., 2011	SZ	75	86	45.7	20%	W: 47% B: 44% H: 5%	-	71.2	18.7	18.4	34.1	505.5	31.0	22.3	5.9	QSU-brief	G – baseline Rw – baseline Re – baseline	0.11 0.05 0.16*
Weinberger et al., 2007	SZ	27	26	41.8	44%	W: 44% B: 48%	12.0	54.7	13.9	12.8	28.1	-	-	21.7	6.6	QSU-brief	G – baseline Rw – baseline Re – baseline	-0.16 -0.19 -0.04
Cannabis														Joint/month				
Dekker et al., 2009	SZ/SZA/SPH/POS	70	61	23.0	0%	-	-	-	-	-	-	-	-	7.6		OCDUS	G – baseline	0.02
Kuepper et al., 2013	SZ/SZA/POS	40	57	37.7	40%	-		1.53	1.73	1.68	-	-	18.1	-		OCDUS	G – baseline	0.39
Schnell et al., 2013	SZ	51	51	26.4	41%	-	-	-	15.2	15.5	-	-	6.0	1.0		CCS-7	G – baseline Rw – baseline Re – baseline	0.21* -0.26 0.35*
Cocaine																		
Carol et al., 2001	SZ	20	20	25.3	-	-	-	-	-	-	-	-	-			VCCQ	G – baseline	0.38*
Smelson et al., 2002	SZ	35	56	42.9	-	W: 9% B: 91%	-	-	-	-	-	-	12.6			VCCQ	G – baseline G – cue exposure	-0.32 0.67*

Table 1. Characteristics and effect sizes (ESr) for the studies included in the meta-analysis.

SZ = schizophrenia ; SZA = schizoaffective disorder ; SPH = schizophreniform disorder ; POS : psychosis no otherwise specified.

CCS-7 : Cannabis-Craving Scale ; FTND = Fagerström test for Nicotine Dependence ; OCDUS : Obsessive Compulsive Drug Use Scale ; QSU : Questionnaire for Smoking Urge ; TCQ : Tobacco Smoking Questionnaire ; Urge VAS = Urge Visual Analogic Scale ; VCCQ : Voris Cocaine Craving Questionnaire.

G = General craving ; Re = Relief Craving ; Rw = Reward Craving ; Baseline = baseline craving condition ; WW = induced withdrawal condition ; Cue = drug-cue exposure condition.

Ethnicity: B= black ; H = hispanic ; NA = native american ; W= white.

* $P < 0.05$.

Type of craving	Condition	Substances	Studies	SUD-SZ	SUD-without-SZ	Effect size				Heterogeneity	
						Zr	95% CI	d	P-value	χ^2	P-value
Global	All conditions	All substances	16	589	630	0.20	[0.15, 0.26]	0.41	P < 0.001	32.27	P < 0.05
	Baseline	All substances	13	527	577	0.15	[0.09, 0.21]	0.30	P < 0.001	43.04	P < 0.001
	Withdrawal	All substances	3	69	73	0.11	[-0.06, 0.28]	0.22	P = 0.21	2.39	P = 0.30
	Drug-cue	All substances	4	70	77	0.41	[0.28, 0.54]	0.90	P < 0.001	14.31	P < 0.05
	All conditions	Tobacco	11	355	390	0.20	[0.13, 0.28]	0.41	P < 0.001	23.34	P < 0.01
	All conditions	Cannabis	3	161	169	0.18	[0.08, 0.30]	0.37	P < 0.001	7.64	P < 0.05
Reward	All conditions	Cocaine	2	55	76	0.23	[0.06, 0.41]	0.47	P < 0.005	1.13	P = 0.28
	All conditions	All substances	7	333	338	0.10	[0.02, 0.17]	0.20	P < 0.05	45.01	P < 0.005
	Baseline	All substances	6	304	312	0.08	[-0.0007, 0.16]	0.16	P = 0.05	45.54	P < 0.001
	Withdrawal	All substances	3	76	77	0.21	[0.05, 0.38]	0.43	P < 0.01	6.51	P < 0.05
	All conditions	Tobacco	7	262	261	0.16	[0.07, 0.23]	0.32	P < 0.005	15.07	P < 0.001
Relief	All conditions	Cannabis	1	51	51	-0.26	-	-0.54	-	-	-
	All conditions	All substances	7	333	338	0.25	[0.17, 0.33]	0.52	P < 0.001	32.27	P = 0.16
	Baseline	All substances	6	304	312	0.30	[0.21, 0.38]	0.63	P < 0.001	25.78	P < 0.001
	Withdrawal	All substances	3	76	77	0.31	[0.15, 0.47]	0.65	P < 0.001	1.43	P = 0.49
	All conditions	Tobacco	7	262	261	0.23	[0.14, 0.32]	0.47	P < 0.001	1.23	P = 0.29
All conditions	Cannabis	1	51	51	0.33	-	0.70	-	-	-	

Table 2: Effect Sizes for each subgroup analyses of studies included in the meta-analysis. Statistical significance ($P < 0.05$) is indicated in bold. *d* refers to Cohen's *d* effect size.