SYSTEMATIC REVIEW

A Research Domain Criteria (RDoC)-Guided Dashboard to Review Psilocybin Target Domains: A Systematic Review

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Abstract

Background Preliminary results from randomized controlled studies as well as identified molecular, cellular, and circuit targets of select psychedelics (e.g., psilocybin) suggest that their effects are transdiagnostic. In this review, we exploit the Research Domain Criteria (RDoC) transdiagnostic framework, to synthesize extant literature on psilocybin.

Objective We aimed to identify RDoC-based effects of psilocybin and vistas for future mechanistic and interventional research.

Methods A systematic search in electronic databases (i.e., PubMed, Scopus, PsycINFO, and Web of Science) performed in January and February 2021 identified English articles published between 1990 and 2020 reporting the effects of psilocybin on mental health measures. Data from included articles were retrieved and organized according to the RDoC bio-behavioral matrix and its constituent six main domains, namely: positive valence systems, negative valence systems, cognitive systems, social processes, sensorimotor systems, and arousal and regulatory systems.

Results The preponderance of research with psilocybin has differentially reported beneficial effects on positive valence systems, negative valence system, and social process domains. The data from the included studies support both short-term (23 assessments) and long-term (15 assessments) beneficial effects of psilocybin on the positive valence systems. While 12 of the extracted outcome measures suggest that psilocybin use is associated with increases in the "fear" construct of the negative valence systems domain, 19 findings show no significant effects on this construct, and seven parameters show lowered levels of the "sustained threat" construct in the long term. Thirty-four outcome measures revealed short-term alterations in the social systems' construct namely, "perception and understanding of self," and "social communications" as well as enhancements in "perception and understanding of others" and "affiliation and attachment". The majority of findings related to the cognitive systems' domain reported dyscognitive effects. There have been relatively few studies reporting outcomes of psilocybin on the remaining RDoC domains. Moreover, seven of the included studies suggest the transdiagnostic effects of psilocybin. The dashboard characterization of RDoC outcomes with psilocybin suggests beneficial effects in the measures of reward, threat, and arousal, as well as general social systems.

Conclusions Psilocybin possesses a multi-domain effectiveness. The field would benefit from highly rigorous proof-of-mechanism research to assess the effects of psilocybin using the RDoC framework. The combined effect of psilocybin with psychosocial interventions with RDoC-based outcomes is a priority therapeutic vista.

1 Introduction

Mental disorders are associated with significant years lived with disability and economic costs across high-income as well as low-income countries [1]. The pharmaceutical companies engaged in drug research and development for mental disorders have prioritized regulatory authorization requirements and as a consequence, clinical trials have enrolled individuals with diagnoses codified according to the *Diagnostic and Statistical Manual of Mental Disorders* and/or *International Classification of Diseases* criteria. Moreover, therapeutic outcomes across mental disorders are determined by change scores on psychometrics that are

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validated for the disorder but are not based on domain-based transdiagnostic outcomes [2].

A consensus exists that the therapeutic innovation stasis in psychiatry is in part owing to the insufficient characterization of the underlying neurobiological processes [3]. The US National Institute of Mental Health proposed the biobehavioral framework, the Research Domain Criteria (RDoC), to characterize brain-based function/dysfunction across multiple units of analysis, extending from genomics to observable behavioral and self-reported characteristics. The RDoC framework conceptualizes psychopathology as transdiagnostic, non-specific to any mental disorder, dimensional, and comprising biological as well as psychological aspects. It is expected that success with RDoC characterization will provide a platform for novel treatment discovery and development in psychiatry [4, 5].

During the past decade, there has been a resurgence of interest in psychedelics as potential treatments for select mental disorders [6, 7]. Psychedelics are a disparate class of serotonergic hallucinogens comprising mechanistically overlapping but dissimilar agents including, but not limited to, psilocybin, mescaline, *N,N*-dimethyltryptamine, and lysergic acid diethylamide [8, 9]. Psychedelics are known to induce a "psychedelic state" characterized generally by altered perception, affect, and cognition [10]. Preliminary results from randomized controlled studies provide evidence that select psychedelics are capable of rapid attenuation of symptoms across some mental disorders (e.g., major depressive disorder, substance use disorder (SUD), anxiety disorders, and trauma-related and stressor-related disorders) [11–15]. The foregoing findings, along with identified molecular, cellular, and circuit targets of select psychedelics (e.g., psilocybin), suggest that their effects are transdiagnostic [16]. Here, we review and synthesize the extant literature evaluating outcomes with psilocybin in accordance with the RDoC framework. The overarching aim of this review is to identify convergent findings with respect to domain-based outcomes with psilocybin interventions as well as inform

hitherto under-evaluated domains. This paper is not intended to be an exhaustive review of the efficacy of psychedelics in psychiatry, as that has been done elsewhere [11].

2 Methods

2.1 Screening Phases I and II

Electronic databases (i.e., PubMed, Scopus, PsycINFO, and Web Of Science) were searched in January and February 2021 using "Psilocybin" as the keyword according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [17]. The period of the search was restricted between 1990 and 2020 for methodological and ethical concerns of the earlier studies on psychedelic substances [18]. Additional studies were added from a manual search of the reference list and Google Scholar. Any animal or human study with an RDoC-compatible outcome measure was included in the review. In the first screening phase, articles were excluded if they were: (i) of irrelevant type of research work, for example, review articles, commentary, conference papers, and case reports; (ii) of irrelevant topics, for example, anthropology, analytical chemistry, botany, and toxicology and safety data; (iii) not available in English; and (iv) not available in full text. In the second screening phase, reviewers checked the compliance of articles' outcome measures with the following proposed definitions of the six main domains provided in the RDoC guideline.

According to the RDoC, the positive valence system (PVS) is a domain that is focused on reward-seeking behaviors, or as put by the RDoC work group, PVS is "primarily responsible for responses to positive motivational situations or contexts, such as reward-seeking, consummatory behavior, and reward/habit learning" [19]. The negative valence system (NVS) is then regarded as the domain that encompasses "responses to aversive situations or context, such as fear, anxiety, and loss" [20]. The cognitive systems domain constitutes a wide range of cognitive processes such as attention, perception, declarative memory, language, and cognitive control [4, 21]. According to RDoC classification, social processes consist of perception and interpretation of "self" and "others," which in turn moderate social communication and a sense of affiliation and attachment [22]. The RDoC framework acknowledges sensorimotor systems as the domain that comprises all the components of control and execution of motor behaviors, such as initiation, execution, and termination of an action [23]. Finally, the arousal and regulatory systems' domain consists of context-related activation and homeostatic regulation [24].

Additionally, studies were excluded if they: (i) were not controlled with an appropriate control condition (in cases of multiple pharmacological interventions, only cross-over

placebo-controlled designs were included); (ii) did not contain an RDoC-compatible finding, i.e., only included diagnostic, as opposed to the transdiagnostic measurements such as Beck Depression Inventory or the Yale-Brown Obsessive-Compulsive Scale; (iii) only included non-domain-specific measurements such as personality traits, head twitch responses, and whole-brain analyses,;(iv) only contained qualitative assessments such as qualitative interviews; (v) only reported correlational analyses; and (vi) contained duplicate data from an included study, i.e., in cases of multiple studies from the same study population, the pertinent data were previously published by an already included study (please refer to Table S1 of the Electronic Supplementary Material [ESM], for the complete list of excluded articles resulted from the second screening phase). The exclusion criteria were also applied to the extracted outcome measures (see below) from the included articles, i.e., outcome measures were included if they met the abovementioned criteria. Therefore, not all of the findings of the included references are listed in the results. Reviewers (i.e., NP, FYS, and ZHK) independently screened articles and their outcome measures based on the inclusion and exclusion criteria and reached a consensus on the final inclusion and classification of the outcomes based on RDoC domains.

2.2 Labeling and Classification of the Extracted Outcome Measures

To form an RDoC-motivated dashboard, outcome measures were extracted from the included studies and were categorized according to the definitions provided by the RDoC framework. To facilitate the data classification, and tabulation, we used a label that contains information about (1) the durability (short-term or long-term assessment, see below) and, if applicable, (2) the directionality of the outcome measure, i.e., an increase or decrease of a scale that assesses the psilocybin-induced changes on a given domain and construct. Outcomes were considered short term if they were taken within 24 hours of drug administration, and long term if the assessment extended beyond this period considering the clearance of psilocybin in humans [25]. The directionality of the findings was defined on a case-by-case basis and according to the associated domain and construct. An example of such labeling is denoting an outcome measure showing long-term enhancement in a given domain, with "le" that stands for "long-term enhancement". In cases where determining the directionality was not possible, such as brain imaging data or an alteration of perception and understanding of "self," the alterations from the control condition were simply denoted in the label as "alteration," for example, short-term alteration in a given domain was denoted by "sa" (for a detailed description of the labels, please refer to Table S2 in the ESM).

After being labeled and classified, the outcome measures were counted in the following manner. (i) The subscales of each analysis method were counted separately if they belonged to disparate domains, for example, "blissfulness" and "anxiety" subscales of the Five-Dimensional Altered States of Consciousness Questionnaire were counted as two separate measures as they belong to PVS and NVS respectively. (ii) If a measurement was taken at two different timepoints, the outcome of each timepoint was labeled and counted separately, for example, State-Trait Anxiety Inventory (STAI) for state anxiety taken in the short term, and in the long term, resulted in two labels. (iii) Different levels of analysis of a given paradigm were labeled differently, for example, reaction time (behavioral) and imaging data assessed within an emotion recognition task were labeled as independent outcome measures.

2.3 Handling the Possible Data Redundancy

In addition to excluding the articles with duplicate data in the screening phase, we identified two other cases of data repetition and hence we took the necessary measures to avoid data redundancy and the consequent data misinterpretation. First, were those cases where multiple studies were performed on the same sample population, for which we have merged the data into one row. Second, those studies that have used different types of methods to assess the same domain and construct, yielding the same results and therefore labels, for example, different self-reports that assess positive mood. In this latter case, we have counted all the identically labeled outcome measures from the same row (study sample) as one label. For instance, in the first row of Table S3 of the ESM, we merged all the studies on the same sample in one row, and also counted all the three outcome measures that showed short-term alterations in the cognitive processes' domain as one "sa" label.

2.4 Introducing Proxy Measures

The current version of the RDoC matrix emphasizes the principles of the framework while adopting a flexible approach to defining the elements of the RDoC matrix, i.e., domains, constructs, and measurements (denoted as units of analysis by the RDoC). In line with this view, the RDoC work group fosters the development of either new or refined matrix elements [26]. Encouraged by this view, we have suggested a number of proxy outcome measures (units of analysis) that we assessed as relevant to the RDoC principles, and denoted them with an asterisk in Table S3 of the ESM (refer to Table S2 of the ESM for a complete list of included outcome measures [units of analysis]).
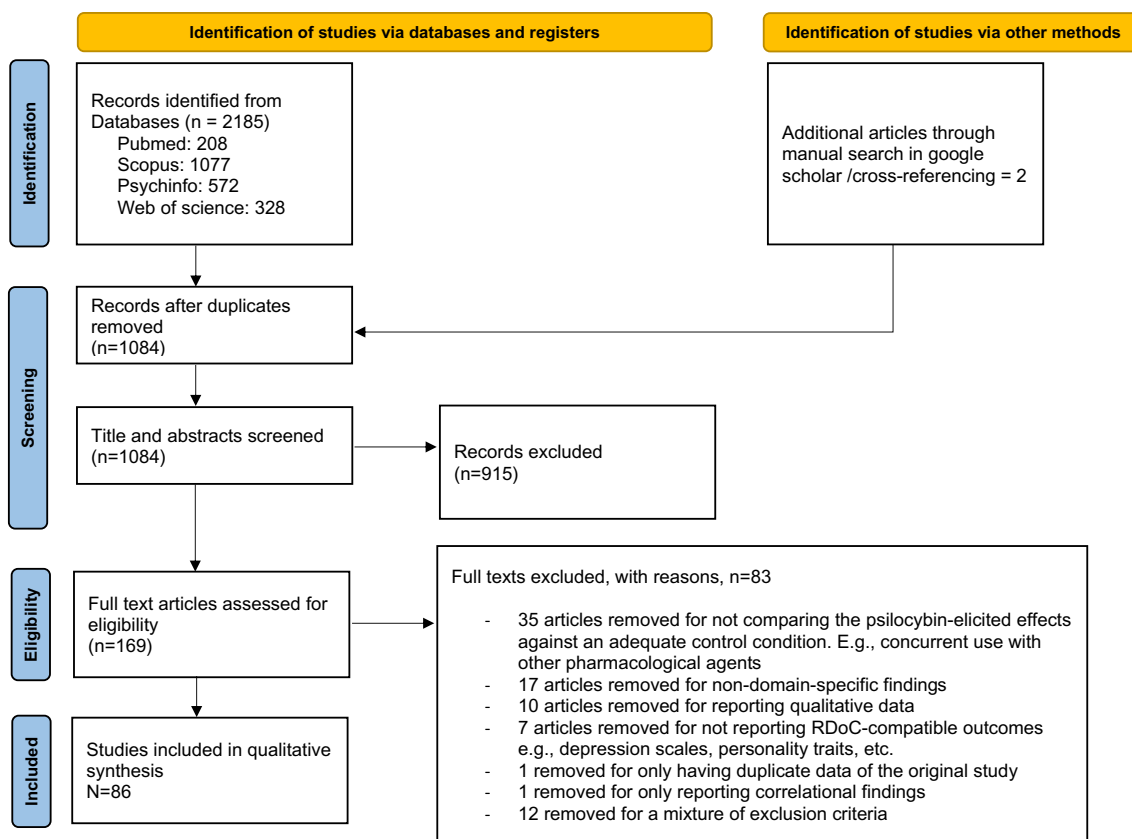
Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram. *RDoC* Research Domain Criteria

3 Results

Eighty-six articles were selected for inclusion (Fig. 1) to which findings a total of 293 labels were attributed, 257 of which were from clinical studies and 36 from preclinical studies (Fig. 2). "Self-reports" were the most-used assessment methods, followed by "paradigms" and "physiology" (Table S2 of the ESM). "Molecules" and "circuits" levels of analysis, which are often derived from the animal studies, were the least investigated levels of analysis (see Sect. 5). As the results provided by these latter levels were diverse, they were labeled as miscellaneous findings (denoted by "m" in Table 1 and in Table S3 of the ESM).

The results formed an RDoC-motivated grid for the effects of psilocybin on different domains and constructs (Table S3 of the ESM). To keep the main text concise, we have transferred Table S3 (RDoC-motivated grid), which contains a large amount of information about the studies, including study design, sample, assessment methods, and the attributed labels, to the ESM. We have subsequently summarized the findings of Table S3 of the ESM in Table 1, which contains information about a given domain's attributed labels, label counts, and the corresponding studies

and study row numbers in Table S3 of the ESM. To gain a detailed overview of the results, we encourage readers to refer to these two tables as they navigate through the result sections. Figure 2 depicts the distribution of the attributed labels across the RDoC domains and, if applicable, constructs. In what follows, we have described the effects of psilocybin in each domain using the label counts.

3.1 Positive Valence Systems

Fifty-seven of the extracted outcomes were assessed as relevant to PVS (Fig. 2). According to the 21 short-term measures obtained from the human studies, such as "blissful state" in the Five-Dimensional Altered States of Consciousness Questionnaire, "positive affect" in the Positive and Negative Affect Schedule, or "joy" in the Mystical-Type Experience Questionnaire self-reports, and 2 outcome measures obtained from the animal studies such as increased time in the feeding zone in response to stressful conditions, psilocybin administration was associated with short-term positive changes in mood and behavior ([27–58], denoted by the label "se" in Table 1 and in Table S3 of the ESM). Moreover, 15 parameters were extracted from studies that evaluated the
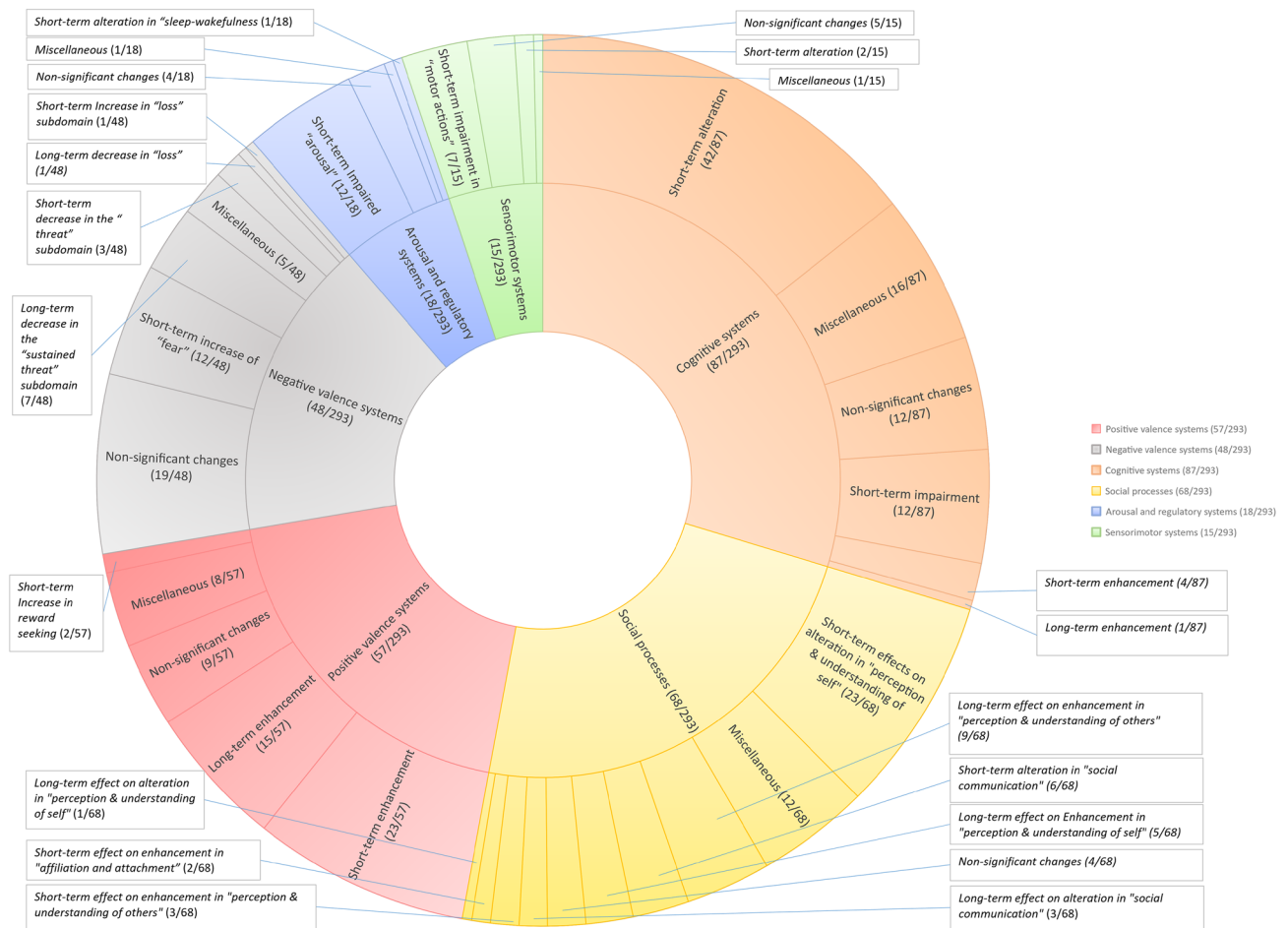
Fig. 2 Distribution of the 293 counted outcome measures across Research Domain Criteria domains (inner wheel). Wherever possible, outcome measures of each domain were classified (inner wheel) by factors such as the assessment time (short-term [< 24 h post-admin-istration] or long-term [beyond 24 h post-administration] measures), direction of alteration, and constituent constructs. The outer wheel depicts the distribution of these classifications

long-term effects of psilocybin on the PVS (denoted by the label "le" in Table 1 and in Table S3 of the ESM). Positive changes in items that were obtained from human studies such as "positive attitudes toward life" and "positive mood changes" in the Persisting Effects Questionnaire, or "vigor" in the Profile of Mood States Questionnaires were measured as late as 6 months after psilocybin intake and reduced "immobility" in response to stressful conditions, 5 weeks post psilocybin administration in an animal behavioral paradigm (forced swimming test), imply durable positive changes in this domain [38–42, 45, 49, 54, 55, 59–72]. The impact of psilocybin on "reward-seeking" behavior was inconsistent. While two parameters imply an increased motivation to re-experience the drug condition (denoted by the label "sir" in Table 1 and in Table S3 of the ESM), two findings show non-significant results. Moreover, the findings from the two clinical studies on the effect of psilocybin on

SUD demonstrate an enhanced functioning of this system (see Sect. 3.7. for more details) [69, 70]. The non-significant findings highlight the crucial role of assessment methods, including appropriate animal models and self-reports, as well as methods of analysis for gauging the effects of psilocybin on the PVS domain [73].

3.2 Negative Valence Systems

The evaluation of the 48 extracted parameters related to the NVS domain suggests that psilocybin mainly affected the constructs "acute threat" and "potential threat" (Fig. 2). Twelve parameters such as "anxiety," "fear," and "tension" from various self-reports, and different paradigms in pre-clinical studies, showed short-term increases in the "acute threat" (fear) construct, which mainly involves immediate responses to aversive stimuli ([27–31, 34–37, 45, 47–49, 55,

Table 1 Efficacy of psilocybin on Research Domain Criteria domains and constructs

Domain	Durability of the effect (short/long term)	Psilocybin-induced alteration in the domain/construct (label)	Number of labels clinical : preclinical	Corresponding rows of the studies in Table S3 (row number of the pre-clinical studies are shown in bold)	References
Positive valence systems	Short term	Enhancement (se)	21:2	1-2-3-5-8-9-12-13-14-16-17-20-21-23-25-28-29-32-35-36-40-**51-53**	[27–58]
		Increase in reward seeking (sir)	1:1	8-**53**	[35–37, 58]
	Long term	Enhancement (le)	13:2	4-10-11-12-13-14-15-17-22-25-27-35-36-**50-52**	[38–42, 45, 49, 54, 55, 59–72]
	NA	Miscellaneous (m)	7:1	6-8-16-22-27-32-39-**51**	[35–37, 43, 44, 53, 57, 67–70, 78, 79, 110]
		Non-significant (NS)	4:5	27-37-39-41-**50-51-52-54-61**	[70–72, 78–82, 139, 140]
Negative valence systems	Short term	Increase in "fear" subdomain (sif)	9:3	1-3-5-8-17-21-23-25-36-**55-56-60**	[27–31, 34–37, 45, 47–49, 55, 74–77]
		Increase in "loss" subdomain (sil)	1:0	8	[35–37]
		Decrease in the "sustained threat" subdomain (sdt)	2:1	12-25-**59**	[39, 40, 49, 83]
	Long term	Decrease in the "sustained threat" subdomain (ldt)	5:2	4-10-11-12-35-**52-59**	[38–40, 54, 59–65, 72, 83]
		Decrease in "loss" subdomain (ldl)	1:0	11	[65]
	NA	Miscellaneous (m)	3:2	32-44-51-**59-60**	[53, 57, 77, 83–85, 85]
		Not significant (NS)	17:2	1-2-8-11-13-16-19-20-23-28-29-32-35-37-39-41-44-**55-59**	[27–32, 35–37, 41, 43, 44, 46, 48, 50–54, 65, 75, 78–88]
Cognitive systems	Short term	Alteration (sa)	40:2	1-2-3-5-7-8-9-12-13-14-15-16-17-19-20-21-23-24-25-27-28-29-30-31-32-33-34-35-36-37-38-39-40-41-43-44-45-46-48-49-**56-57**	[27–32, 34–37, 39–56, 66, 70, 74, 76, 78–82, 84–92, 97–105]
		Impairment (si)	11:1	8-30-31-37-38-39-41-42-43-44-46-**58**	[35–37, 78–82, 84, 85, 88–96]
	Long-term	Enhancement (se)	4:0	14-33-35-47	[42, 54, 106, 107]
		Enhancement (le)	1:0	14	[42]
	NA	Miscellaneous (m)	15:1	3-7-8-15-19-24-29-30-31-32-33-38-39-46-48-**56**	[33, 35–37, 51–53, 66, 76, 78, 79, 86, 87, 89, 92–94, 97, 98, 101, 103, 106]
		Not significant (NS)	11:1	7-8-24-29-30-31-38-39-43-47-49-**58**	[35–37, 51, 52, 78, 79, 89–91, 93, 94, 96–98, 101, 104, 107]

Table 1 (continued)

Domain	Durability of the effect (short/long term)	Psilocybin-induced alteration in the domain/construct (label)	Number of labels clinical : preclinical	Corresponding rows of the studies in Table S3 (row number of the preclinical studies are shown in bold)	References
Social processes	Short term	Alteration in "perception & understanding of self" (sas)	23:0	1-2-3-5-7-8-9-13-16-17-19-20-21-23-25-28-29-32-35-36-44-45-48	[27–32, 34–37, 41, 43–55, 74, 84–88, 97–100, 102, 103, 108]
		Enhancement in "perception & understanding of others" (seo)	3:0	8-14-20	[35–37, 42, 46]
		Alteration in "social communication" (sasc)	6:0	4-10-16-28-29-32	[38, 43, 44, 50–53, 59–64, 100]
		Enhancement in "affiliation and attachment" (sea)	2:0	18-23	[48, 109]
	Long term	Alteration in "social communication" (lasc)	3:0	4-10-12	[38–40, 59–64]
		Alteration in "perception & understanding of self" (las)	1:0	36	[55]
		Enhancement in "perception & understanding of self" (les)	5:0	12-13-17-25-36	[39–41, 45, 49, 55]
		Enhancement in "perception & understanding of others" (leo)	9:0	10-12-13-14-15-17-22-25-36	[39–42, 45, 49, 55, 66–69, 99]
	NA	Miscellaneous (m)	12:0	4-5-6-8-14-19-20-23-26-32-45-48	[34–37, 42, 46, 48, 53, 59–64, 86, 87, 102, 103, 110, 111]
		Non-significant changes (NS)	4:0	14-16-20-29	[42–44, 46, 51, 52, 100]
Arousal and regulatory systems	Short term	Impaired "arousal" (sia)	12:0	8-13-17-25-27-29-36-37-38-39-40-41	[35–37, 41, 45, 49, 51, 52, 55, 56, 70, 78–82, 89]
		Alteration in "sleep-wakefulness" (ssw)	1:0	7	[97, 98]
	NA	Miscellaneous (m)	1:0	39	[78, 79]
		Non-significant changes (NS)	4:0	7-8-36-39	[35–37, 55, 56, 78, 97, 98]
Sensorimotor systems	Short term	Alteration (sa)	0:2	**51-57**	[57, 105]
		Impairment in "motor action" (sim)	4:3	8-19-25-37-**50-56-60**	[35–37, 49, 71, 76, 77, 80, 81, 86, 87]
	NA	Miscellaneous (m)	0:1	**56**	[76]
		Non-significant changes (NS)	1:4	16-**52-54-55-57**	[43, 44, 72, 75, 100, 105, 139]
Total:			257:36		

NA not applicable

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74–77], denoted by the label "sif" in Table 1 and in Table S3 of the ESM). In contrast, 19 findings from both clinical and animal studies demonstrate non-significant effects of psilocybin on "acute threat" [27–32, 35–37, 41, 43, 44, 46, 48, 50–54, 65, 75, 78–88]. Additionally, seven self-reports, such as STAI, showed decreases in "sustained threat," assessed both in the short term, on day 1, and longitudinally ([38–40, 49, 54, 59–65, 72, 83] denoted by the labels "sdt" and "ldt" in Table 1 and in Table S3 of the ESM).

3.3 Cognitive Systems

Eighty-seven outcome measures pertained to the cognitive systems' domain, five of which were obtained from animal studies (Fig. 2). Psilocybin alters the functioning of the cognitive domain's constructs namely perception, attention, cognitive control, and memory, as reported by 54 objective and subjective measures deployed in the selected articles. Twelve of these measures suggest that psilocybin impairs cognitive functioning ([35–37, 78–82, 84, 85, 88–96], denoted by the label "si" in Table 1 and in Table S3 of the ESM) and the rest of the measures demonstrate a shift from the normal waking cognitive functioning ([27–32, 34–37, 39–56, 66, 70, 74, 76, 78–82, 84–92, 97–105], denoted by the label "sa" in Table 1 and in Table S3 of the ESM). Aside from the majority of the reports of short-term cognitive impairment and alteration, four short-term and one long-term outcome measures suggested that psilocybin could have enhanced cognitive abilities ([42, 54, 106, 107], denoted by the label "se" and "le" in Table 1 and Table S3 of the ESM) such as improving autobiographical memory and creativity scales as assessed both in the short and long term [42, 106].

3.4 Social Processes

The social processes domain was amongst the most studied domains with varying levels of analysis that enabled a more detailed overview of how psilocybin affected each of the constituent constructs. In total, 68 outcome measures were extracted for this domain, all from clinical studies (Fig. 2). Thirty-four measures gauged the short-term effects of psilocybin on social processes, 23 of which assessed how psilocybin alters the "perception and understanding of self" ([27–32, 34–37, 41, 43–55, 74, 84–88, 97–100, 102, 103, 108], denoted by the label "sas" in Table 1 and in Table S3 of the ESM), three demonstrate enhancements in the "perception and understanding of others" ([35–37, 42, 46], denoted by the label "seo" in Table 1 and Table S3 of the ESM), six reported changes in the "social communication" ([38, 43, 44, 50–53, 59–64, 100], denoted by the label "sasc" in Table 1 and Table S3 of the ESM), and two outcome measures showed enhancements in the "affiliation and attachment" construct ([48, 109], denoted by the label

"sea" in Table 1 and Table S3 of the ESM). Eighteen assessments further tested the long-term impact of psilocybin in social processes, five of which demonstrated enhancements ([39–41, 45, 49, 55], denoted by the label "les" in Table 1 and in Table S3 of the ESM and one showed alterations in "perception and understanding of self" ([55], denoted by the label "las" in Table 1 and in Table S3 of the ESM), nine informed on enhancements in "perception and understanding of others" ([39–42, 45, 49, 55, 66–69, 99], denoted by the label "leo" in Table 1 and in Table S3 of the ESM), and three displayed variations in the "social communication" cluster ([38–40, 59–64] denoted by the label "lasc" in Table 1 and in Table S3 of the ESM). Twelve parameters categorized as miscellaneous ([34–37, 42, 46, 48, 53, 59–64, 86, 87, 102, 103, 110, 111], denoted by the label "m") were mainly correlational findings and four parameters indicated outcome measures that remained unchanged by psilocybin (denoted by the label "ns").

3.5 Sensorimotor Systems

From the 15 outcome measures that represented the effect of psilocybin on the sensorimotor systems, seven reported short-term impairment in "motor action" via monitoring motor behaviors in different paradigms such as locomotor behavior during the open-field test or the motor praxis task in clinical studies ([35–37, 49, 71, 76, 77, 80, 81, 86, 87], denoted by the label "sim" in Table 1 and in Table S3 of the ESM). In contrast, three studies that investigated the effect of psilocybin on locomotor behavior in animal models demonstrated no effects of psilocybin on this feature [72, 75, 139].

3.6 Arousal and Regulatory Systems

The 13 clinical outcome measures related to regulatory and arousal systems mainly imply that the administration of psilocybin is associated with a short-term decrease in vigilance related to the "arousal" construct (12 findings denoted by the label "sia" in Table 1 and in Table S3 of the ESM, [35–37, 41, 45, 49, 51, 52, 55, 56, 70, 78–82, 89]) as well as acute alterations in sleep patterns (one parameter denoted by the label "ssw" in Table 1 and in Table S3 of the ESM [97, 98]).

3.7 Transdiagnostic Effects of Psilocybin

In addition to investigating the effects of psilocybin on disparate domains and constructs, seven clinical studies included in this review also reported the efficacy of psilocybin in different diagnostic categories. In an open-label study, Carhart-Harris and colleagues investigated the effects of two doses of psilocybin (10 and 25 mg) on patients with treatment-resistant depression [64]. Compared with baseline measurements, this study revealed significant improvements

on different depression and anxiety assessment instruments scales such as the Beck Depression Inventory, STAI, Hamilton Depression Rating Scale, and Montgomery–Åsberg Depression Rating Scale, in the follow-up timepoints. Their primary outcome measure, the Quick Inventory of Depressive Symptoms, showed improved scores in 1 week, 2 weeks, 3 weeks, 5 weeks, and 3 months following the intervention. In another study, Anderson and colleagues investigated the effects of adjunctive psilocybin administration (0.3–0.36 mg/kg) to group therapy on the demoralization scale in long-term survivors of acquired immune deficiency syndrome [65]. Their results show significant improvement in the demoralization scale 3 months following the intervention compared with baseline.

Three clinical studies investigated the effects of psilocybin-assisted psychotherapy in cancer-related anxiety and depression. Grob and colleagues performed a pilot, double-blind, placebo-controlled study using 0.2 mg/kg of psilocybin [54]. Their preliminary results revealed significant improvements in anxiety, as shown by the STAI scale at 1-month and 3-month follow-up points, and marked mood improvement as assessed by the Beck Depression Inventory scale 6 months post-intervention. In a double-blind cross-over clinical trial, Ross and colleagues showed that a single dose of psilocybin-assisted psychotherapy induces rapid and sustainable improvements in anxiety, depression, demoralization, hopelessness, and spiritual well-being in patients with cancer, as measured immediately and at 6.5-month follow-up [40]. In another clinical trial ran by Grffiths and colleagues, the effects of single high-dose psilocybin (22 or 30 mg/70 kg) were controlled with low-dose psilocybin (22 or 30 mg/70 kg) in cancer-related mood disorders [49]. Similar to the other two studies mentioned above, the results of this clinical trial revealed rapid and sustainable psilocybin-induced improvements in mood-related assessments such as quality of life, life meaning, optimism, and death as measured during the study, and at a 6-month follow-up. The remaining included studies probed the effects of psilocybin on SUDs. In two consecutive studies, Johnson and colleagues investigated the short-term and long-term effects of psilocybin-assisted psychotherapy on smoking cessation [67, 69]. Their results reveal a significantly reduced number of cigarette consumption (assessed by timeline follow-back data of self-reported daily smoking), lowered temptation (measured by the Smoking Abstinence Self-Efficacy scale), and craving (measured by the Questionnaire on Smoking Urges) to smoke at a 10-week, 6-month, 12-month, and 30-month post-psilocybin-facilitated smoking cessation program. Finally, in an open-label clinical study, Bogenschutz assessed the effects of psilocybin-assisted motivational enhancement therapy on alcohol dependence [70]. Psilocybin significantly reduced the drinking days (as measured by timeline follow-back data of self-reported daily alcohol

consumption) and drinking temptation (assessed by the Penn Alcohol Craving Scale and Alcohol Abstinence Self-Efficacy Scales), and increased self-confidence for alcohol abstinence (assessed by the Alcohol Abstinence Self-Efficacy Scale).

4 Discussion

Using a dashboard to synthesize and illustrate the extant literature for psilocybin underscores its trans-domain effects (Table S3 of the ESM). Moreover, the evidence has differentially reported on aspects of NVS, PVS, and social domains. There was a relatively low number of articles evaluating the sensorimotor and arousal and regulatory systems.

In parallel to reviewing the multi-domain effectiveness of psilocybin, we have suggested incorporating additional self-reporting and/or objective measures solicited by the selected articles that could inform on any of the RDoC domains. In what follows, we have summarized the findings for each domain.

4.1 Positive Valence Systems

As demonstrated in the dashboard and the corresponding Fig. 2, psilocybin has mood-enhancing effects starting post-administration, that are sustainable for weeks, and are projected on mood and behavioral measures. In addition to healthy volunteers, this profile is also seen in patients with a variety of *Diagnostic and Statistical Manual of Mental Disorders* categories, such as cancer-related anxiety, SUD, and major depressive disorder [54, 64, 67, 69].

The abnormality in the PVS domain is seen across multiple mental disorders such as MDD and SUD [112, 113]. For instance, self-report measures of PVS, including but not limited to measures of experiential and anticipatory anhedonia, indicate a deficit in these systems in persons with depression and post-traumatic stress disorder [114, 115]. Most of the standard treatment candidates, such as serotoninergic antidepressants, fail to demonstrate a significant efficacy on this specific reward-processing abnormality [116–118]. Thus, any intervention that shows superior efficacy in this domain could be a promising candidate in treatment-resistant conditions. Therefore, the promising findings of the possible benefits of psilocybin on the PVS call for complementary studies to elaborate on the accurate profile, temporality, and durability of the therapeutic trajectory and its translation to other mental disorders.

4.2 Negative Valence Systems

The data in this review reveal distinct effects of psilocybin on disparate NVS constructs. In the "acute threat" construct, psilocybin seems to induce "acute threat" responses as

demonstrated by 12 cases. However, 19 parameters suggest that the "acute threat" construct is unaffected by psilocybin. Factors such as dose, time of the measurement, and context seem to contribute to this variability [44, 57]. Another main finding was that psilocybin administration was mainly associated with decreases in the "sustained threat" construct as measured by STAI questionnaires. These results have important clinical implications, especially when considering administering psilocybin to the susceptible population as the transient "acute fear" induced by the drug varies amongst individuals and necessitates accompanying psychological support during administration [28]. The few studies that investigated the effects of psilocybin on the NVS at molecular and circuits levels of analysis (denoted by label "m" in Table 1 and in Table S3 of the ESM) yielded diverse and therefore inconclusive results. Further proof-of-mechanism studies are essential to gain a systematic understanding of the interaction between psilocybin at molecule and circuit levels of assessment (see limitations).

The malfunctions associated with the NVS domain consist of altered aversive stimuli perception and responses, present in anxiety-related disorders such as post-traumatic stress disorder and general anxiety disorder [119, 120]. Ongoing clinical studies on psychedelic effects on NVS-related problems warrant a closer look at how psychedelics might affect this critical system. For instance, the promising benefits of psilocybin on the measures of "sustained threat" encourage complementary mechanistic research on this construct. Moreover, further research is needed to understand how confounding factors, such as psychotherapy, affect the variability of the acute anxiogenic symptoms [121].

4.3 Cognitive Systems

In general, understanding the cognitive systems' domain is tightly linked to our knowledge of human consciousness [10, 122–124]. As the nomenclature of "psychedelics" implies, these agents alter cognition and perception and create a psychosis-like state [10]. Thus, they are becoming a popular tool to study human consciousness for a wide range of scientists with diverse interests from philosophy to clinical implications of consciousness on mental health.

The RDoC-motivated grid for psilocybin, not surprisingly, shows a robust short-term alteration of cognitive functions as assessed by different levels of analysis such as self-reports, behavioral paradigms, and neuroimaging measures. The cognitive-altering phenomenon associated with psychedelics motivated several researchers to study how psychedelics target the cognitive domain, and to explore the possible mechanisms underlying visual perception in normal populations as well as hallucinations, which is the hallmark of disorders like schizophrenia [90, 92, 95]. The forgoing cognitive alterations, similar to other acute effects,

are reported to fade after the peak psychedelics experience, while some reports suggest enduring and lasting perception problems as side effects [125]. Therefore, investigating such reports with the help of longitudinal studies is essential for characterizing the safety profile of these agents.

Apart from cognitive impairment, researchers have also taken interest in evaluating the possible cognitive enhancement properties of psychedelics, which has long motivated consuming psychedelics in popular culture and was recently suggested to have a positive role clinically, such as facilitated psychotherapy [126, 127]. The two studies assessing the cognitive enhancement potential of psilocybin showed improvements in cognitive abilities such as autobiographical memory and creative thinking [42, 106]. Considering the importance of this subject on clinical as well as public health decisions, more proof-of-concept studies are warranted.

4.4 Social Processes

Deficits in different constructs of the social processes' domain can lead to impaired interpersonal relationships. For instance, impaired emotional or cognitive empathy, impaired facial processing, or "reception of facial communication" present as core dysfunctions of many psychiatric problems [50, 128–130].

Denoted as "entactogens" or "empathogens," the use of psychedelics is associated with a specific experience of "oneness" or "unity" with a greater entity—a unique phenomenon thought to result from an alteration of "self" [8, 10]. A considerable number of the included articles report alterations, and in some cases enhancements, of the "perception and understanding of self" construct by psilocybin [45, 49]. Psilocybin also seems to have positive short-term and long-term effects on the "perception and understanding of others" construct, which is demonstrated in increases in empathy and compassion as measured by subjective measures [35–37, 39–42, 45, 46, 49, 55, 66–69, 99]. An enhancement of "social affiliation and attachment" was also observed following psilocybin administration, which is demonstrated by a lowered feeling of social exclusion in the cyberball task, and decreased inequity aversion in the ultimatum game paradigm [48, 109].

As for the objective measures, researchers have commonly used a variety of emotion recognition paradigms, which mostly enable a closer look at the "social communication" construct at the neural circuit level of analysis [38, 43, 44, 50–53, 59–64, 100]. Interestingly, the few articles that studied the circuits and behaviors in patients showed contrasting results from those of healthy volunteers. For instance, Stroud and colleagues showed a decreased reaction time to emotional stimuli in patients, while other articles suggest increased reaction times in healthy volunteers [60]. Another example is the work of Roseman and colleagues

who suggested an increased amygdala reactivity to fearful faces, which was positively associated with the favorable clinical outcome; a finding opposite to those of healthy volunteers where it is often suggested that psilocybin decreased amygdala reactivity to facial stimuli [62]. Taken together, the data in the RDoC grid imply that psilocybin might have a novel target on the social processes' domain, which necessitates more proof-of-mechanism and crossover studies with the existing therapeutic interventions.

4.5 Sensorimotor Systems

The limited amount of existing data suggests that psilocybin administration is followed by a transient slowing motor function. These alterations should be taken into consideration in assessments that involve motor functions such as reaction time (see [80, 81, 131]). Evidently, this understudied domain requires more studies characterizing the role of psilocybin in the function of the sensorimotor system.

4.6 Arousal and Regulatory Systems

On a general level, psilocybin seems to immediately reduce vigilance, which is demonstrated in less responsivity to questions or perhaps lower task engagement, and hence might influence behavioral paradigms. The only study that investigated the sleep patterns reported that psilocybin intake was associated with prolonged rapid eye movement sleep latency and decreased rapid eye movement duration (trending non-significant) [97]. An altered function in the arousal and regulatory systems domain is often observed in individuals with a range of psychiatric problems such as depression [132]. Considering the clinical importance and the limited number of works on the effects of psilocybin in the arousal and regulatory systems, this domain remains unexplored.

4.7 Transdiagnostic Effects

Exploring the possible mechanism of the transdiagnostic characteristics of psychedelics was one of the main goals of this systematic review. The few studies included in our review imply that psilocybin might have a transdiagnostic target. Accordingly, this review has also shown that psilocybin can benefit multiple domains and constructs, which might further benefit those disparate diagnostic categories with shared dysfunctions across disparate domains and constructs. In support of this view, Kelly and colleagues have also gauged the transdiagnostic potential of psychedelics through the RDoC lens, positing that multidomain effectiveness might explain why these agents seem to be effective in disparate diagnostic categories [16]. Another recent review has proposed a different hypothesis, which focuses on the

psychedelics' ability to induce neuronal and mental plasticity as a booster to psychotherapy-induced change mechanisms and subsequent transdiagnostic targeting [133]. Future clinical trials and proof-of-mechanism research endeavors will shed light on the psychedelics' dynamics across mental health disorders.

5 Limitations

The findings of this review should be considered in light of some limitations. The main limitation of this review was that none of the included studies was designed in terms of RDoC, and consisted of a wide variety of methods, samples, and goals to gauge the effects of psilocybin. Given the novelty of both the RDoC framework and psychedelic research, such diversity of methods and research goals certainly benefits the progress of psychedelic research. Nonetheless, accumulating the results of these studies in the RDoC framework should be considered as a preliminary review according to the best judgment and understanding of the authors about the relevance of each outcome measure to the RDoC constructs and domains.

Another limitation of this review was combining the results of studies with multiple designs (e.g., randomized and non-randomized clinical studies), aiming at providing an exhaustive overview of the effects of psilocybin on the RDoC domains. Thus, the synthesis of the current results should be viewed with caution in terms of probable biases concerning the heterogeneous study design and hand-picked outcomes, subgroups, and reported analyses [134].

The other limitation concerned the inconclusive data from the animal studies included in this review. As can be seen in Table 1, only a few of the animal studies rendered a conclusive overview of the dynamics of psilocybin in each domain, which is mainly because this area is rather underdeveloped [135]. Animal models have the potential to shed light on molecular mechanisms and neural circuits that underlie the psychedelic-behavioral, cognitive, and affective modulations. Therefore, there is an urgent need for developing fit-to-purpose validated animal models in psychedelic research with an appropriate selection of design, execution, and outcome measures [73, 135, 136].

Despite these limitations, this review reveals the potential of employing multifaceted frameworks, such as the RDoC, to parse the complexity of psychedelics' effect on neurobehavioral functioning. To further develop such a framework for psychedelics research, there is a demand for studies examining particular RDoC constructs. Such studies are then able to carefully choose the specific tasks that would be most relevant to the study aim and would further need to develop more tasks and paradigms as a precursor [26]. An example of such paradigms already proposed by RDoC

is the effort expenditure reward task, which is designed to measure the "effort" subconstruct of the "reward valuation" construct in the PVS domain. Currently, there is a need for more studies with psilocybin using the foregoing validated measures contemporaneously with neuroimaging to convincingly establish a proof of mechanism. Studies by Pokorny and colleagues and Barret and colleagues are good examples of where behavioral and self-report levels of analysis are supported by neuroimaging data [38, 46]. Novel techniques such as machine learning could also be solicited to integrate disparate units of analysis [137, 138].

6 Conclusions

In this review, we categorized the data reported by a selected number of articles according to the RDoC classification. The RDoC-motivated grid demonstrates transdiagnostic findings for psilocybin and indicates promising evidence for its benefits in the PVS, NVS, and social systems—domains underserved by current treatments for mental disorders. The profile also reveals a gap of knowledge in the drug's interaction with the sensorimotor and arousal systems, and a more fine-grained view of its effectiveness on the proposed sub-constructs of each domain using observable and self-report paradigms that are validated with respect to their nomological properties and performance across disparate subdimensions [2]. In conclusion, the RDoC framework presents a compelling platform to gain a mechanistic view on psilocybin, which paves the way for individualized and transdiagnostic use of this pharmacological agent for mental health problems.

Declarations

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