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REVIEW

A century of research on psychedelics: A scientometric analysis on trends and knowledge maps of hallucinogens, entactogens, entheogens and dissociative drugs

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Abbreviations: LSD, Lysergic acid diethylamide; DMT, Dimethyltryptamine; MDMA, 3,4-methylenedioxymethamphetamine; PCP, Phencyclidine; NPS, Novel psychoactive substances; GHB, Gamma-hydroxybutyric acid; PTSD, Post-Traumatic Stress Disorder; WOSCC, WOSCC Web of Science Core Collection.

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Abstract
A scientometric analysis was realized to outline clinical research on psychedelics over the last century. Web of Science Core Collection was searched up to March 18, 2022, for publications on psychedelics. Network analyses and bibliometrics were combined, to identify research themes and trends with Bibliometrix and CiteSpace. The primary aim was to measure research trends evolution over time, and the secondary aims were to identify bibliometric performance and influence networks of publications, authors, institutions, and countries. Sensitivity analyses were conducted for 2016-2022, and 2021 time periods. We included 31,687 documents (591,329 references), which aggregated into a well-structured network with credible clustering. Research productivity was split into an early less productive period mainly focusing on safety issues, and a "psychedelic renaissance" after the 1990s. Major trends were identified for hallucinogens/entheogens, entactogens, novel psychoactive substances (NPS), and on dissociative substances. There was a translational evolution from the bench to the bedside, with phase 2 and 3 trials and/or evidence synthesis in particular. The most recent trends concerned NPS, ketamine-associated brain changes, and ayahuasca-assisted psychotherapy. The USA and Canada were the most productive settings for the research overall, and more recently this geographical distribution became more prominent, reflecting legislative context/policy making. A translational evolution of psychedelics has been occurring, that has brought approval of esketamine for depression and will likely lead to approval of additional psychedelics across mental and physical conditions. Toxicology screening tools for NPS are urgently needed, which in turn might follow the same translational evolution of psychedelics in the future.

1. Introduction

Plant-based psychedelics, such as psilocybin, ayahuasca, ibogaine or peyote have an ancient history of traditional healing practices and religious use, remarkably clustered on the American continent (Carod-Artal, 2015). The first wave of modern research into psychedelics dates back to the end of the 19th century, with the first experiments involving peyote by American and European physicians and pharmacists. Its active ingredient, mescaline, was isolated and identified in 1894 by the German chemist and pharmacist Arthur Heffter, then synthesized in 1919 by the Aus-

trian chemist Ernst Späth. This allowed the development of medical research in North America and Europe, within the framework of a 'psychotomimetic' paradigm: mescaline was then seen as a chemical agent to induce model psychoses (Jay, 2020). However, while the German psychiatrist and neurologist Kurt Beringer had postulated in 1927 that transient mescaline-induced psychoses could provide access to the experiences of some patients, the possibility of using mescaline for the treatment of depression had already been suggested by French psychiatrists Henri Ey and Henri Claude (H. Ey and Claude, 1934).

The discovery of the effects of the lysergic acid diethylamide (LSD) in 1943 (Hofmann, 1980) and the rediscovery of Mexican divinatory mushrooms in 1953 (R. Heim, 1958) led to extensive medical research on serotonergic hallucinogens, with a switch from the psychotomimetic to the 'psychedelic' paradigm (Osmond, 1957).

However, this research dried up from 1966 onwards, due to a combination of factors. The issue first arose in 1962 amid the thalidomide scandal (Oram, 2018), combined to a moral panic linked to the use of drugs during the Vietnam War in the United States (USA) (Dyck, 2008), with 'very mixed feelings on psychedelic research' as expressed by Jonathan Cole (USA Congress, 1962), and following experiments conducted at Harvard without institutional approval (Pahnke, 1969). Nevertheless, since the late 80s, there was a second wave of research on psychedelics that has been referred to as a 'psychedelic renaissance' (Sessa, 2012) with numerous publications in the field of neurobiology and neuroscience (Carhart-Harris and Goodwin, 2017; Kelly et al., 2019). Initial clinical trials focused on the benefits of psilocybin to reduced anxiety and improve mood of patients with cancer (Griffiths et al., 2016; Grob et al., 2011). Additional psychedelics have been tested in conjunction with psychotherapy for the treatment of suicidal thoughts (Witt et al., 2020), anxiety and depression (Carhart-Harris et al., 2021; Palhano-Fontes et al., 2019), addiction (Bogenschutz et al., 2015; Winkelman, 2014), and for Post-Traumatic Stress Disorder (PTSD) (Mitchell et al., 2021; Moreno et al., 2006). More recently, work has reported on neuroimaging findings (Abdallah et al., 2017; Daws et al., 2022), and current studies are underway for patients with chronic anorexia nervosa (NCT04052568) and obsessive-compulsive disorder (NCT03356483).

This significant growth in the literature requires new approaches to review and analyze trends within the knowledge domain. Scientometrics - i.e., bibliometrics when applied to science research - allows one to summarize large amount of bibliometric data in order to present the state of knowledge and emerging trends of a research topic over time. Distinct from the systematic review, scientometric analysis mainly uses co-cited articles to extract clusters of highly cited articles, revealing research trends and influence networks. A scientometric approach shows how networks of research topics, keywords, authors, journals, countries, institutions, and authors have evolved over time.

To date we have identified three published bibliometric studies in the field: the Khalili and colleagues 2018 bibliometric analysis on illicit drugs for the 1995-2014 time period (Khalili et al., 2018), the Lawrence and colleagues 2021 study on 'top-cited articles on classical psychedelics' that describes an 'older' and a 'recent cohort' of clinical trials on classic psychedelics (Lawrence et al., 2021), and the Hadar and colleagues 2022 bibliometric analysis that produced a comprehensive science mapping confined to the top-cited 100 articles of the last 30 years, with a focus on the intellectual structure of research (Hadar et al., 2022). None of these studies applied a scientometric approach which included both a measure of research trends and hotspots on psychedelics over time, in addition to purely bibliometric performance analysis. The aim of the present paper is to fill this gap.

2. Materials and methods

2.1. Primary and secondary objectives

With this first comprehensive scientometric study, the primary objective was to analyze how research trends on psychedelics have evolved over decades. The secondary objective was to measure research performance/influence and relevance in terms of countries, institutions, authors, and journals.

The study protocol can be found on Open Science Framework (osf.io) (link). It is based on a previous published large-scale scientometric analysis (Sabe et al., 2022), and was informed by the concept of 'research weaving' proposed by Nakagawa and colleagues, a new framework for research synthesis of both evidence and influence, accounting for trends over time (Nakagawa et al., 2019).

2.2. Included and excluded drugs

Based on clinical experience, and a comprehensive list of psychedelics (www.psychonautwiki.org/; camh.ca), it was a-priori decided to focus on drugs with clinically relevant safety issues or therapeutic potential, and the focus was deliberately narrowed on hallucinogens/entheogens (LSD, N,N-Dimethyltryptamine (DMT), ayahuasca, psilocybin, mescaline, peyote, ibogaine), entactogens: 3,4-methylenedioxymethamphetamine (MDMA), dissociative anesthetics (ketamine), phencyclidine (PCP), and novel psychoactive substances (NPS) (e.g. phencyclidine-type substances, plant-based substances).

We did not include those drugs which present psychedelics effects, but are essentially psychostimulants or sedatives, or that constitute a separate class of drugs due to their specific actions, such as cannabis, amphetamines, psychostimulants, dextromethorphan, gamma-hydroxybutyric acid (GHB), cocaine, khat, heroin and alcohol. Furthermore, some medications that could be misused to provoke psychedelics effects were not included, such as memantine, atropine, biperiden. A glossary of selected subclass of psychedelics is available as supplementary information 1.

2.3. Search strategy and data collection

The Web of Science Core Collection (WOSCC) was explored using different keywords and medical subject headings, such as 'psilocybin', 'ketamine' or 'LSD'. Considering the focus on clinical research, several terms not relevant to psychedelics or human studies were excluded. The full list of search terms is available in the published protocol. There were no limitations on language, time or populations. The database source was limited to Science Citation Index Expanded, publication types to articles, reviews and proceedings papers. Irrelevant categories (e.g., astronomy) and meeting abstracts were also excluded. Reasons for exclusion are presented in the flow-chart (Supplementary Fig. 1). The full records with cited

references were retrieved on March 18, 2022, into tag-delimited plain text files. WOS highly cited papers are papers that rank in the top 1% by citations for field and year. All highly cited papers were inspected, as a random sample of 10% of the dataset, as described in our protocol. Duplicates were identified with CiteSpace.

2.4. Data analysis

The Bibliometrix R package (3.1.4) (Aria and Cuccurullo, 2017) was used to extract information on authors and journals. CiteSpace (version 6.1. R3) (Chen, 2006) was used to extract co-citation analyses (for co-cited references, co-authors countries, institutions, co-authorship networks), co-occurrence networks (authors' keywords), and conduct burstness analyses. Citation counts are the number of direct citations to a publication. Co-citation analysis extracts pairs of papers that are cited together in the source articles (Small, 1973), and co-occurrence networks count paired data within a collection unit.

Co-cited network and co-occurrence networks are both undirected graphs. Different units of measure were therefore used: author, journal, reference, country, institution, and keyword. For co-cited analyses, the most suitable author-level metric is the g-index, as compared to the h-index, the latter presents more sensitivity to poorly- as to highly-cited papers (Egghe, 2006). Of importance, CiteSpace optimizes time slicing by excluding empty intervals of the retained timeframe. CiteSpace parameters are reported in supplementary information 2.

CiteSpace uses different network analyses, with structural (betweenness centrality, modularity, silhouette score) and temporal metrics (citation burstness), as a combination of both (sigma metrics). Betweenness centrality is a measure of centrality in a graph based on shortest paths, representing the degree to which nodes relate to each other (Freeman, 1977). Nodes with the highest betweenness centrality are generally at the center of networks and tend to go to the value 1.

Two other structural metrics are essential to CiteSpace, the modularity score (Q score) that measures the strength of division of a network into clusters, and the silhouette score (S score) that calculates the goodness of a clustering technique (Shibata et al., 2009). Q scores range from 0 to +1, the S scores range from -1 to +1, and for both metrics, a score close to +1 represents the best clustering model. For Q values greater than 0.3, the cluster structure is considered significant, and higher values may indicate a well-structured network; when the silhouette coefficients exceed 0.3, 0.5, or 0.7, the network is considered homogenous, reasonable, or highly credible, respectively. Nevertheless, a silhouette score of 1 may indicate that a cluster is isolated. Cluster labels are generated by CiteSpace from noun phrases of the keyword lists of articles cited in each cluster using the likelihood ratio test ($p<0.001$). Furthermore, temporal metrics are used, such as burstness that measures the rate of change, detecting over a specific time period when important changes in the frequency of event occurs (Kleinberg, 2003). CiteSpace determines the combination of both betweenness centrality and citation burstness in a metric called sigma. Sigma is computed as $(\text{centrality} + 1)^{\text{burstness}}$ (Chen, 2006), with higher values indicating higher influential potential.

Finally, CiteSpace employs structural variation analyses to measures the relative structural change due to the information from published paper with reference to a baseline network, therefore identifying potential transformative papers (Chen, 2012).

3. Results

3.1. References retrieved

Our dataset retrieved 41,135 documents. Following the data filtering process detailed in our protocol, 19% of the total documents were excluded (Supplementary Fig. 1). The final dataset retained 31,867 documents (28,579 articles; 3,288 reviews) cumulating 591,329 references from 2,809 different sources (e.g., journals, books). Articles in 22 different languages were found, with 95.5% being in English. On the 168 highly cited articles and 10% of the randomly selected articles, less than 3% of the articles were non-relevant (Supplementary Table 1).

The first identified paper is the Carter paper from 1901 on three case of poisoning mushrooms (Carter, 1901). The analysis of scientific production on psychedelics reveals two essential time periods. The first time period with a mean annual growth rate of 4.97% from early 1900 to 1990, and a peak of 171 articles published in the year 1974 shortly after the 'war on drug' USA global campaign (Fig. 1, Supplementary Fig. 2). The second time period from 1990 to date, corresponds to the 'psychedelics renaissance', and presents a still ongoing increase of publications, with a mean annual growth rate of 7%: 190 publications in 1990 to 1,538 in 2021, and from 1 to 4.1 average citation per year (Supplementary Fig. 3). Consistently, initial clinical trials on lysergic acid diethylamide (LSD) and psilocybin ceased in mid-70s, and restarted around year 2000 (Supplementary Fig. 4).

The scientific output presented a first peak with 174 publications in 1971; however, the number of publications plateaued at 130 publications per year until 1990 with 190 publication, and 408 in 1991.

The average citation per document is 31.5 citations, and the average citation per year plateaued from 1920 to 1975 between 0.4 to 0.8, before an exponential raise from 0.6 in 1980, to 2.7 in 2000, and 4.5 in 2016 (Supplementary Fig. 2).

3.2. The co-cited reference network

3.2.1. Clusters of research: 1950-2022 time period

The co-cited reference network reveals research trend evolutions, clusters and hotspots. We extracted the co-cited reference network with details of clusters for the 1950-2022 time period (Fig. 1); corresponding burstness and time map as shown in Supplementary Fig. 5A and B, respectively. Furthermore, to scrutinize the most recent trends, we retrieved the 2016-2022 and year 2021 co-cited reference networks (Supplementary Fig. 6.A.B and 7.A.B respectively). Details of each cluster were closely inspected to establish whether the generated labels were adequate or needed relabeling (Supplementary Fig. 5.C, 6.C and 7.C). A video of the link walkthrough between clusters can be found on osf.io (link).

For the period 1950-2022, we identified 31 different clusters, of which 26 aggregated into a single constellation with a well-structured network (Q=0.919) and highly credible clustering (S=0.975). The 2016-2022 and 2021 periods also presented well-structured networks and highly credible clusters (Q=0.688, S=0.916 and Q=0.527, S=0.842).

The link walkthrough between clusters based on burstness dynamic permit to identify two major trends of research, Trend I and Trend II (Fig. 1). The first one on 'hallucinogens/entheogens, entactogens, novel psychoactive substances (NPS)' (from left to right, clusters #8, #4, #18, #7, #22, #12, #14, #1, #16, #3, #11 and #15), and the second one on the use of, and the neuroscience involving 'substances

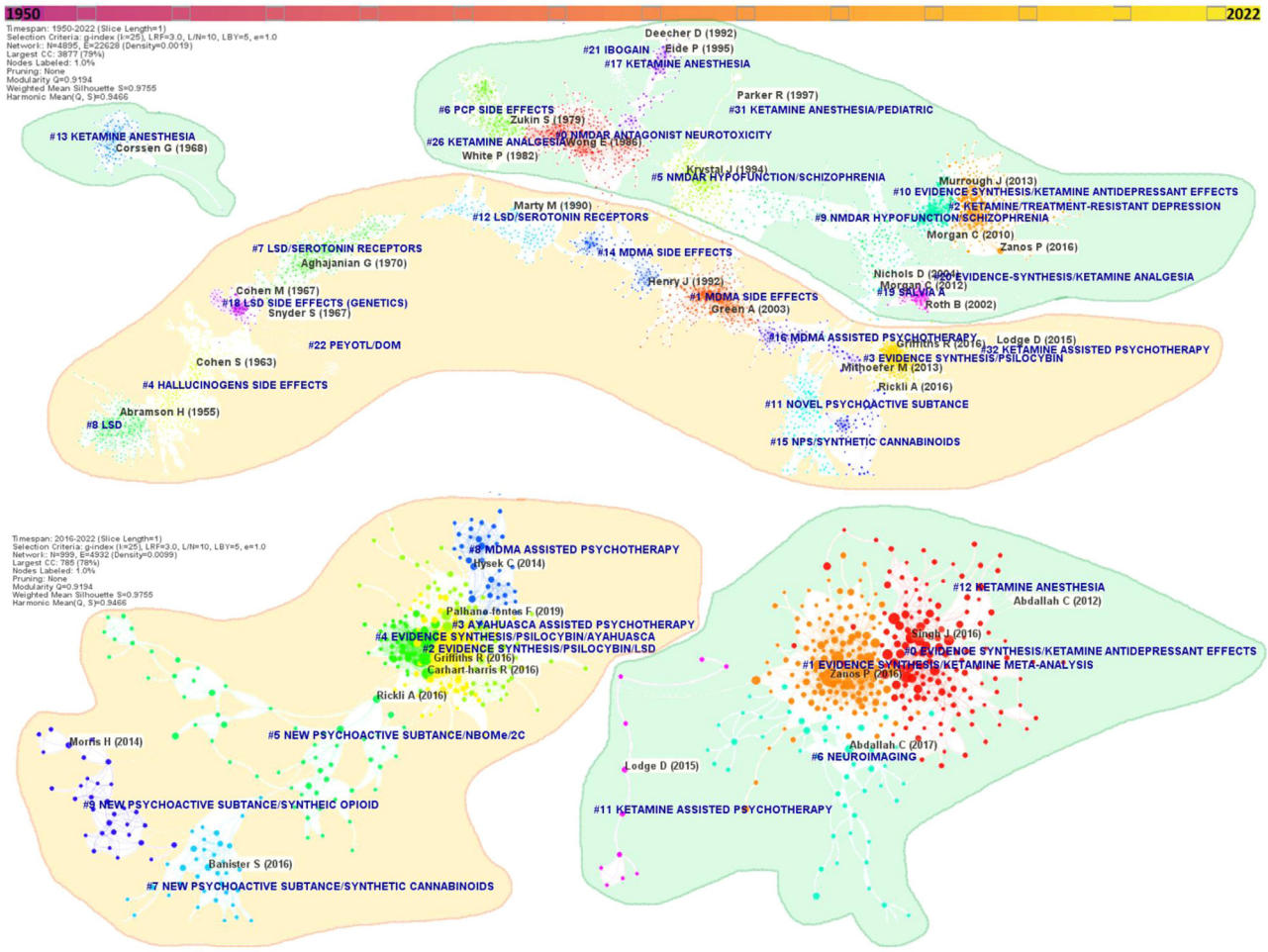

Fig. 1 Co-cited reference networks for the 1950-2022 (A) and the 2016-2021 (B) time periods with highlight of clusters: Trend I 'hallucinogens/entheogens, entactogens, novel psychoactive substances (NPS)' (orange) and Trend II 'substances with dissociative properties' (green). The position of the node (article) corresponds to the year of publication. The size of a node is proportional to the number of times the node has been co-cited. For each cluster, a single color is attributed. For Figure 1.A, each cluster is arranged on a horizontal timeline from left (1950) to right (2022). For the Figure 1.B, time trend is only linked to colors.

with dissociative properties' (clusters #13, #26, #6, #0, #21, #17, #5, #31, #9, #19, #10, #20, #2, and #32). Importantly, both research trends recently ended in evidence-synthesis clusters.

We detail below the cluster label, the cluster silhouette score (S), size (N), mean year (Y) of co-cited articles, and the most representative reference for each trend.

The first trend on 'hallucinogens/entheogens, entactogens, NPS' starts with research on LSD, cluster 'LSD' #8(S=0.996; N=194; Y=1954) (Abramson et al., 1955). LSD is the main drug of interest in the next emerging clusters, which focus on 'hallucinogens side effects' #4 (S=0.973; N=243; Y=1961) (Cohen, 1960), and 'LSD side effects (genetics)' #18(S=0.996; N=79; Y=1967) (Cohen et al., 1967). This cluster #4 is rejoined by a distinct cluster on 'peyotl/2,5-dimethoxy-4-methylamphetamine' #22 (S=0.996; N=56; Y=1967) (Snyder et al., 1967). This predominance of research on LSD continues with a focus on pharmacological aspects 'LSD/serotonin receptors' that encompass both cluster #7 (S=0.987; N=219; Y=1974) (Bennett and Snyder, 1976), and #12 (S=0.993; N=124; Y=1986) (Titeler et al., 1988).

This predominance of research on LSD ends in the 1990s with a decade of research on 3,4-methyl enedioxy methamphetamine (MDMA) reflected throughout 'MDMA side effects', cluster #14 (S=0.993; N=116; Y=1990) (Henry et al., 1992), and cluster #1 (S=0.969; N=325; Y=2001) (Green et al., 2003).

The literature then started to focus on efficacy, initially psychedelics assisted-psychotherapy for patients presenting PTSD, 'MDMA assisted psychotherapy' #16 (S=0.982; N=95; Y=2010) (Mithoefer et al., 2013), which was effective in four phase 2 trials (NCT00090064, NCT01211405, NCT01793610, NCT00353938) and one phase 3 trial (NCT03537014) for PTSD (Feduccia et al., 2019; Jerome et al., 2020; Mitchell et al., 2021; Mithoefer et al., 2019, 2018, 2013, 2011; Oehen et al., 2012). This wide body of research on assisted-psychotherapy, escalated over the last two decades, with the emergence of evidence syntheses, in particular research on psilocybin, 'evi-

dence synthesis/psilocybin' #3 (S=0.981; N=273; Y=2016) (Griffiths et al., 2016). We also found increasing research on diverse 'novel psychoactive substance' #11 (S=0.954; N=175; Y=2011) (Prosser and Nelson, 2012), and more recently work on synthetic cannabinoids 'novel psychoactive substance/synthetic cannabinoids' #15 (S=0.994; N=96; Y=2015) (Rickli et al., 2016).

The second trend starts in the 1970s, with initial research on 'ketamine anesthesia'#13 (S=0.996; N=119; Y=1970) (Corssen, 1968), and in the 1980s with 'ketamine analgesia'#26 (S=0.997; N=22; Y=1979) (White et al., 1982). Then, research evolves into pharmacological research on phencyclidine (PCP) animal models, 'PCP side effects' cluster #6 (S=0.983; N=219; Y=1979) (Zukin and Zukin, 1979), which is also connected with cluster #12. Soon after, cluster #6, the cluster with the greatest number of highly co-cited papers, namely 'N-methyl-D-aspartate receptor (NMDAR) Antagonist neurotoxicity' #0 (S=0.952; N=329; Y=1987) (Olney et al., 1991) appears. The research on NMDAR is connected with four small clusters #17, #21 and #31, #19. Cluster #17 is 'ketamine anesthesia' #17 (S=0.995; N=88; Y=1994) (Eide et al., 1995), clinically close to 'ketamine anesthesia/pediatric' #31 (S=1; N=12; Y=1996) (Parker et al., 1997). Cluster #21 is on 'ibogain' #21 (S=0.982; N=64; Y=1993) (Deecher et al., 1992) linked to the NMDA antagonist actions of ibogaine, with putative 'anti-addictive' properties, potentially mitigating opioid dependence. Cluster #19 is on 'Salvia A', considered in anesthesia as a kappa-opioid selective agonist, #19 (S=0.995; N=72; Y=2006) (Roth et al., 2002). The most obvious development of cluster #0, are cluster #5 and #9 on 'NMDAR hypofunction/schizophrenia', #5 (S=0.986; N=230; Y=1996) (Moghaddam et al., 1997), #9 (S=0.95; N=183; Y=2005) (Patil et al., 2007), structured around a model of schizophrenia that is complementary to the classical dopamine hypothesis of schizophrenia. Beyond schizophrenia, the role of dissociative agents has also recently been investigated in depression, with clusters #2 and #10, 'ketamine/treatment-resistant depression'#2 (S=0.937; N=284; Y=2016) (Singh et al., 2016) and 'evidence synthesis/ketamine antidepressant effects', #10 (S=0.965; N=178; Y=2011) (Murrough et al., 2013a), and 'ketamine assisted psychotherapy' #32 (S=0.999; N=11; Y=2016) (Dore et al., 2019). Finally, a further evidence synthesis cluster on 'evidence synthesis/ketamine analgesia' #20 (S=0.988; N=71; Y=2006) (Morgan et al., 2010) is visible, confirming the convergence on meta-research in this field.

In order to identify the latest trends of research, we further analyzed the 2016-2022 and the 2021 co-cited reference network (Supplementary Fig. 6, 7). For the 2016-2022 network, we identify two additional clusters, one on 'ayahuasca-assisted psychotherapy/microdosing' #35 (S=0.867; N=66; Y=2018) (Palhano-Fontes et al., 2019) and one on 'neuroimaging/ketamine' #5 (S=0.951; N=52; Y=2016) (Abdallah et al., 2017). For the 2021 network, we also identify two additional clusters 'psychedelic-assisted therapy/ anorexia nervosa' #5 (S=0.823; N=32; Y=2018) (Foldi et al., 2020), and 'intranasal ketamine for acute pain' #10 (S=0.99; N=5; Y=2018) (Bouida et al., 2020).

3.2.2. Most cited papers and burstness analyses

We extracted the top 10 most cited papers for the 1950-2022 co-cited reference network (Table 1). The top three co-cited papers were Griffiths and colleagues 2016 randomized-controlled trial (RCT) of psilocybin use for life-threatening cancer patients with depression and anxiety (Griffiths et al., 2016), Carhart-Harris and colleagues 2016 open-label feasibility study on psilocybin assisted psychotherapy for treatment-resistant depression (Carhart-Harris et al., 2016), and Nichols review on psychedelics (Nichols, 2016).

Further, the burstness analyses for the 1950-2022, 2016-2022 and 2021 co-cited reference networks (Supplementary Table 2.E.F.G.H.I.J) show that over the last five years, the three papers with the most important strength of burst for the 2016-2022 network were: Murrough and colleagues 2013 RCT on ketamine in treatment-resistant major depression (Murrough et al., 2013a); Murrough and colleagues 2013 open-label on rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression (Murrough et al., 2013b); and Zarate and colleagues 2012 RCT replicating of ketamine's antidepressant efficacy in bipolar depression (Zarate et al., 2012).

For the 2021 year, the most significant papers were the following: Ochs-Ross and colleagues 2020 RCT on esketamine added to antidepressant in elderly patients with treatment-resistant depression (Ochs-Ross et al., 2020); Zheng and colleagues 2018 open-label study on repeated-dose intravenous ketamine for patients with unipolar and bipolar depression (Zheng et al., 2018); and Wilkinson and colleagues 2018 meta-analysis on the effect of a single dose of intravenous ketamine on suicidal ideation (Wilkinson et al., 2017).

In order to detect transformative papers, we conducted a structural variation analysis for the 2016-2021 and the 2021 time periods (Supplementary Table 3). The three papers with the most transformative potential for the 2016-2022 network were: McMilan and colleagues 2020 RCT on simultaneous EEG/fMRI recorded during ketamine infusion in patients with major depressive disorder (McMillan et al., 2020); Fan et al. 2017 RCT on ketamine use for acute suicidal ideation in cancer patients (Fan et al., 2017); and Yao et al. 2021 animal study on pathways in microglia underlying antidepressant-like effects of I-ketamine (Yao et al., 2021). Similarly, for the 2021 time period, the three most transformative papers were: Inserra and colleagues 2021 review on prescribing psychedelic compounds as medications (Inserra et al., 2021); Okada and colleagues 2020 review on prevention of ketamine-induced neuropsychiatric adverse reactions (Okada et al., 2020); Palamar and colleagues 2020 review on drug screening for novel psychoactive substances (Palamar et al., 2020).

3.3. Co-occurring authors' keywords network

WOS includes keywords from 1991 on. For our dataset, a total of 33,657 author's keywords were identified. We extracted the co-occurring authors' keyword network (2016-2022) to reveal insights into knowledge structures and obtain the temporal dynamics of latest research trends. The

Table 1 The top 10 most co-cited references.

Number of co-citations in the network/ Number of citations in the literature[a]	Year	Source	Vol	Page	Title	Doi	Type of study	Related cluster in Fig. 1
259/1002	2016	J Psychophar-macol	30	1181-1197	Griffiths et al. 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial	10.1177/0269881116675513	RCT	2
236/853	2016	The Lancet	3	619-627	Carhart-Harris et al. 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study	10.1016/S2215-0366(16)30065-7	open-label feasibility study	1
228/818	2016	Pharmacol Rev	68	264-355	Nichols, 2016. Psychedelics	10.1124/pr.115.011478.	Review	3
224/997	2013	Am J Psychiatry	170	1134-1142	Murrough et al. 2013. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial	10.1176/appi.ajp.2013.13030392	RCT	0
224/804	2016	J Psychophar-macol	30	1165-1180	Ross et al. 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial	10.1177/0269881116675512	RCT	3
178/913	2016	Nat Med	22	238-249	Duman et al. 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants	10.1038/nm.4050	Review	0
159/726	2012	Biol Psychiatry	71	939-946	Zarate et al. 2012. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial	10.1016/j.biopsych.2011.12.010	RCT	0
158/455	2018	Pharrmacol Rev	70	621-660	Zanos et al. 2018. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms	10.1124/pr.117.015198	Systematic review	2
155/650	2013	Biol Psychiatry	74	250-6	Murrough et al. 2013. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression	10.1016/j.biopsych.2012.06.022.	Clinical trial	2
152/966	2010	JAMA Psychiatry	67	793-802	Diazgranados et al. 2010. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression	10.1001/archgenpsychiatry.2010.90.	RCT	2
151/445	2015	Am J Psychiatry	172	950-66	Newport et al. 2015. Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression	10.1176/appi.ajp.2015.15040465.	RCT	2

[a] Number of citations in the literature according to the journal where the paper was published.

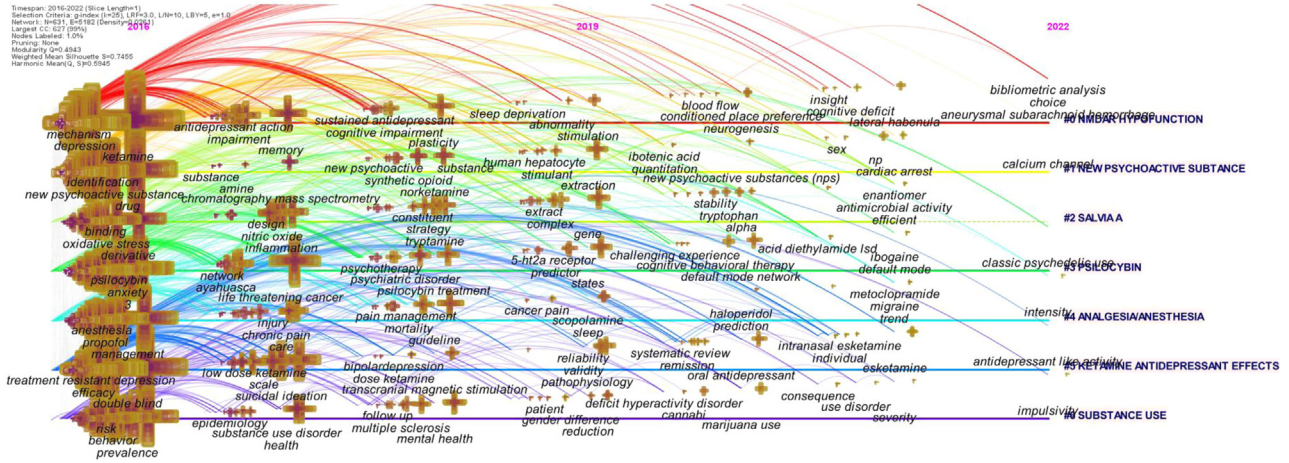

Fig. 2 Timeline visualization of co-occurring authors' keywords networks (2016-2022). The nodes (keywords) are represented with crosses. The size of a cross is proportional to the burstness of keyword co-occurrence. The co-occurrence network is weighted on total link strength across different keyword nodes and scored on the average publication years. The clusters are labeled at the far right of the timeline maps, with a different color for each cluster.

network gathered seven clusters with an acceptable modularity score (Q=0.494) and a significant silhouette score (S=0.745) (Fig. 2).

The first and most prominent cluster was 'NMDAR hypofunction' #0 (S=0.68; N=123; Y=2017), followed by 'novel psychoactive substance' #1 (S=0.824; N=100; Y=2017), 'salvia A' #2 (S=0.684; N=92; Y=2018), 'psilocybin' #3 (S=0.677; N=90; Y=2017), 'analgesia/anesthesia' #4 (S=0.744; N=75; Y=2017), 'ketamine antidepressant effects' #5 (S=0.834; N=75; Y=2017), 'substance use' #6 (S=0.78; N=57; Y=2017). Moreover, the results of the burstness analysis found that the latest (2020-2022) most cited keywords ranked by beginning of burst were 'oral antidepressant', 'default mode network', 'multiple sclerosis', 'psilocybin treatment' and 'cognitive behavioral therapy' (Supplementary Table 2.P.Q).

3.4. Analysis of cooperation networks across countries and institutions

Collaboration networks are based on countries, institutions and groups of authors. We identified 141 different co-authors' countries, with the countries with the greatest number of publications being the USA (n=11,288; 35.4% of total articles), the United Kingdom (n=2,818; 8.84%), Germany (n=2,275; 7.14%), and China (n= 1,812; 5.68%). These countries presented in the same order 8669, 2028, 1734 and 1439 citations (Supplementary Table 4).

We generated the collaborative country network with extraction of the network of co-authors' countries (Fig. 3A). The modularity score was significant, and the silhouette suggested highly credible clusters (Q=0.4973; S=0.9279). The network shows important betweenness centrality for European countries, Japan, Brazil and the USA. China occupies a central place with a recent escalation in citations. The burstness analysis revealed that the countries with the highest strength of citation were China (2018-2022), the USA (1980-1990) and Turkey (2007-2014) (Supplementary Table 2.B).

The research network gathered 16,162 institutions. The three institutions with the highest number of publications were University of California (n=929), the National Institutes of Health USA (n=770), and the University of London (n=740).

We retrieved the co-cited institution network for the 2016-2022 time period that retained 450 institutions (Fig. 4). The modularity score was significant, and the silhouette suggested highly credible clusters (Q=0.4235; S=0.7901). The 2016-2022 burstness analysis found that the top three institutions with the strongest strength of citation were the National University of Singapore (2021-2022), the University Health Network (Toronto) (2021-2022) and the Canadian Rapid Treatment Center of Excellence (Toronto) (2021-2022) (Supplementary Table 2.D).

3.5. Analysis of co-authorship network

We identified 73,664 authors with a mean of 2.75 authors per articles, and when present 4.68 co-authors per articles. We retrieved the 1950-2022 authors' collaborative network with the co-authorship networks that permitted visualization of the scientific collaboration between authors by using the frequency of co-authorship. This network presented a significant modularity (Q=0.9733), and a very high silhouette score indicating the relative isolation of groups of co-authors (S=0.9918) (Supplementary Fig. 8). We identified 21 different clusters. The most recently active clusters were #5 'research on ketamine antidepressant effects' (S=1; N=78; Y=2009), #4 'research on novel psychoactive substances' (S=0.99; N=82; Y=2013), and #36 'datura metel' (S=0.99; N=13; Y=2017).

The burstness of co-authorship for the 1950-2022 network (Supplementary Table 2.H) shows that the three co-authors with the most important strength of citation burst were

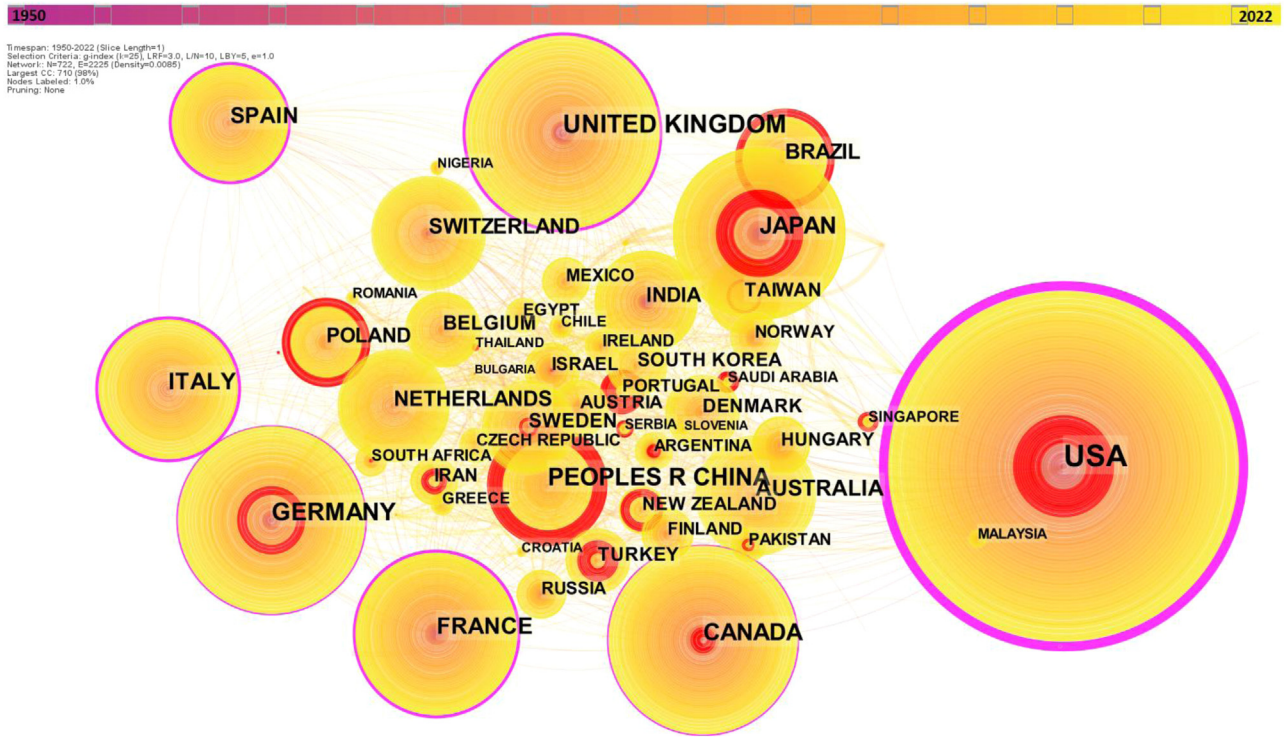

Fig. 3 Network of co-authors' countries (1950-2022). Betweenness centrality organize the network. The position of the nodes (countries) correspond to the mean year of publication. Co-citation is revealed with the presence of yellow tree rings, proportional to the number of co-citation. Burstness of citation is revealed with the presence of red tree rings, which superimpose the co-citation rings. The outermost purple ring denotes the centrality level, and highly central nodes are considered pivotal points in the research field. We limited the nodes to the 60 first countries.

Zarate CA (2012-2022), Carhart-Harris RL (2013-2022), and Roth BL (2003-2013).

3.6. Analysis of co-cited journals

We identified 2,560 different journals in our dataset, with the highest number of relevant papers being published in Psychopharmacology (n=483), Forensic Science International (n=355), and Journal of Psychopharmacology (n=324) (Supplementary Fig. 9 and Supplementary Table 5). We extracted the network of co-authors journal network (1950-2022) that uses as unit the authors' co-cited journals. This network reveals the macro-structure of scholarly disciplines through analysis of journal titles (Supplementary Fig. 10). The modularity score was significant, and the silhouette suggested highly credible clusters (Q=5265; S=0.831). Seven cluster were identified: the first cluster, #0 'anesthesiology journals' encompassed the greatest number of co-citations, followed par #1 'psychiatry/neurology/neuroscience journals', #2'chemistry journals', #3'pharmacology journals', #4'toxicology journals', #5'forensic/chemistry journals', and #6'addictology journals'.

The 1950-2022 network reveals that the three journals with the highest strength of citation burst were Journal of Pharmacology and Experimental Therapeutics (1950-1999), Life Science (1975-1999), and European Journal of Pharmacology (1975-2002) (Supplementary Table 5). Furthermore, the three journals with the most recent burst of citation were The Lancet Psychiatry (2017-2022), Translational Psychiatry (2017-2022), and Journal of Affective Disorders (2017-2022).

4. Discussion

4.1. Summary of the main findings

To the best of our knowledge, this is the first broad scientometric analysis that presents a comprehensive overview of the trends in clinical research for hallucinogens, entactogens, entheogens and dissociative drugs. This study included 31,867 documents, mostly published in English, encompassing more than half a million references. Findings clearly identify two time periods of scientific interest and productivity on psychedelics, a first time block peaking in 1974 with a low annual growth of publications (mean 5%), then a pause due to the "war on drug", then a "psychedelic renaissance" after 1990, and progressive increase of productivity from 190 publications in 1990 to 1538 in 2021.

4.2. Insights on most recent research trends

We identified 26 clusters that aggregated into a network, with two main research trends, namely one on hallucinogens/entheogens, entactogens, NPS, and one on substances

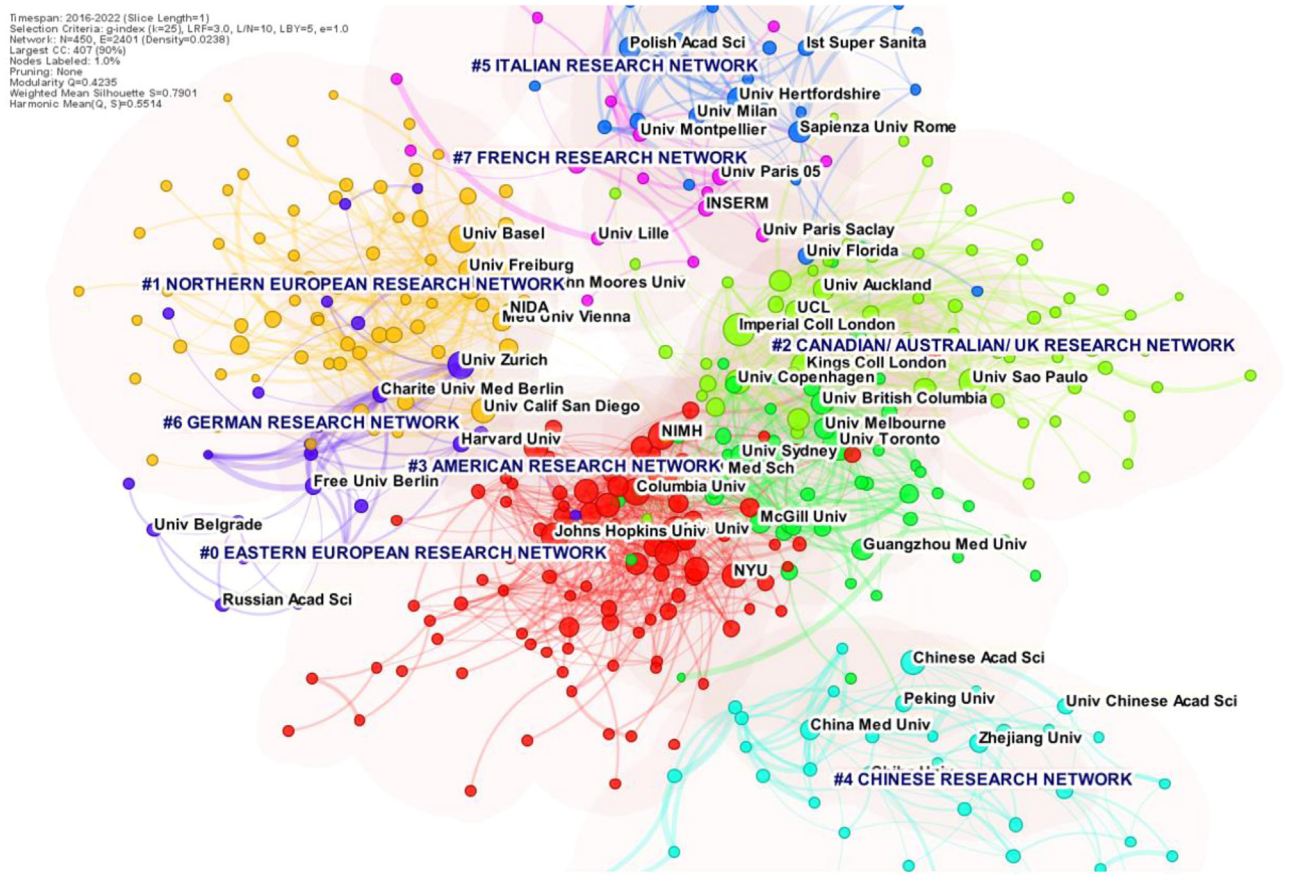

Fig. 4 Network of co-authors institutions with highlights of the clusters (2016-2022). Each node represents an institution. Each cluster gathers several institutions that constitute a research network. The thickness of links between nodes is proportional to the intensity of collaboration and denotes of the influence of each node. Betweenness centrality organize the network with most influent institutions being at the center of the network.

with dissociative properties, that recently evolved in evidence synthesis clusters.

In the first trend (hallucinogens/entheogens, entactogens, NPS) saw an evolution from LSD effects to the therapeutic potential of MDMA and psilocybin, as well as toxicity of NPS. Consistent with the bench to bedside translational journey of psychedelics, the most cited studies where on the clinical use of psilocybin in people with both physical (cancer and depression or anxiety) (Griffiths et al., 2016) and mental (depression) disorders (Carhart-Harris et al., 2016). Indeed, evidence has been accumulating on the efficacy of psychedelics in depression and PTSD. Specifically, in depression several phase 2 trials have been completed, with very promising results; both ayahuasca (Palhano-Fontes et al., 2019) and psilocybin (NCT03181529) (Davis et al., 2021) outperformed placebo, and psilocybin was also non-inferior to escitalopram (NCT03429075) (Carhart-Harris et al., 2021). For PTSD, MDMA-assisted psychotherapy outperformed control condition in as many as four phase 2 trials (NCT00090064, NCT01211405, NCT01793610, NCT00353938) and one phase 3 trial (NCT03537014) (Feduccia et al., 2019; Jerome et al., 2020; Mitchell et al., 2021; Mithoefer et al., 2019, 2018, 2013, 2011; Oehen et al., 2012). Beyond these positive results in depression and PTSD, additional clinical testing has stemmed from the successful results described above, with new randomized controlled trials investigating psychedelics in anorexia nervosa, and pain (Bouida et al., 2020; Foldi et al., 2020). These two further potential applications of psychedelics are of great importance in medicine. Anorexia nervosa is a mental disorder with several physical complications (Solmi et al., 2016a, 2016b, 2015) and high mortality (Steinhausen, 2009) that affects typically, but not only, young women (Solmi et al., 2021a), and for which there still no clear gold-standard treatment, and, importantly, for which there is still no indicated medication (Solmi et al., 2021b). Chronic pain is frequently not sufficiently managed by available medications, leading opioid prescription (Kalkman et al., 2019), and the well-known excess of deaths, and costs (Barocas et al., 2022; Brady et al., 2017). Novel medications with novel mechanisms of action are urgently needed for both these disorders.

Regarding the second trend, on substances with dissociative properties, we found a progressive evolution over time from ketamine use in anesthesia, to a PCP model for schizophrenia, and then to the therapeutic potential of NMDA receptor modulation across different mental disorders including schizophrenia and depression. For this second trend, the clinical application of dissociative substances generated the most impactful research, specifically

on the application of ketamine in subjects with treatment-resistant unipolar or bipolar depression (Feeney et al., 2021; Murrough et al., 2013a, 2013b; Ochs-Ross et al., 2020; Wilkinson et al., 2017; Zarate et al., 2012; Zheng et al., 2018). After the FDA approved intranasal esketamine for the treatment of resistant depression (Papakostas et al., 2020; Singh et al., 2020), in addition to the frequent use of esketamine, both intravenously and intranasally, for resistant depression (Fava et al., 2020; McIntyre et al., 2020), additional research has focused on targeting bipolar depression. Recently, ketamine outperformed placebo in a phase 2 trial targeting suicidal ideation (NCT01944293). Beyond mood disorders, ketamine has also been tested in alcohol use disorder with promising (day of abstinence), yet not convincing (no difference on relapse rates) results in a phase 2 trial (NCT02649231) (Grabski et al., 2022), as well as in cocaine use disorder with improvement of motivation to quit and craving in a phase 2 trial (NCT01790490) (Dakwar et al., 2014).

When taking a closer look at the very most recent trends of the translational shift of psychedelics and dissociative substances from pharmacology to clinical testing, some further transformative trends emerged, again consistent with the two identified research trends. From the first trend, a transformative trend toward clinical testing of psilocybin, and toxicology screening for novel psychoactive substances, was evident. NPS are increasingly available on the illegal market, can be easily bought online, and have potentially catastrophic effects on human health (Schifano et al., 2021). NPS are frequently used in the context of other substance of abuse, with associated serious health risks including mortality (Webb et al., 2022). Clinicians have been shown to have only limited knowledge of how to detect NPS (Dal Farra et al., 2022; Ramos et al., 2020), which poses important clinical concerns regarding the management of overdose from NPS. For instance, synthetic opioids can have longer half-life compared with prescribed or intravenous opioids, and clinicians who are not aware of such differences can miss scheduling repeated naloxone doses to avoid respiratory depression in subjects with signs of opioid overdose. The trend on toxicology screening for NPS well reflects the need for clinicians, in particular those working in emergency setting with their frantic and unpredictable routine, of having promptly available screening tools that effectively detect NPS (Giorgetti et al., 2022; Klingberg et al., 2022), which prompts initiatives in the context of national and international networks (Heyerdahl et al., 2014; Partridge et al., 2021; Smith et al., 2022).

From the second trend, novel research was aimed at better understanding the neural correlates of ketamine's effects, including its impact on neural activity (McMillan et al., 2020) and microglia (Yao et al., 2021), as well as testing its safety (Okada et al., 2020), and efficacy in patients with cancer and those with intense suicidal ideation (Fan et al., 2017).

4.3. Influence networks and changes in policy

Of interest, the clinical evolution of psychedelic research is reflected in the shift in the target journals, with increasing numbers of publications in journals focused on translational or clinical psychiatry (i.e. The Lancet Psychiatry, Translational Psychiatry, Journal of Affective Disorders). For instance, several highly cited publications from The Lancet journals focused on trials testing psilocybin or MDMA in clinical populations including PTSD and depression (Carhart-Harris et al., 2016; Mithoefer et al., 2018, 2016; Short et al., 2018), but also beyond mental disorders including use of intraoperative ketamine to prevent delirium (Avidan et al., 2017). Similarly, in Translational Psychiatry and Journal of Affective Disorders several reports focused on efficacy and safety of ketamine and its enantiomers (Bahji et al., 2021; Correia-Melo et al., 2020; Ionescu et al., 2019; Yang et al., 2019, 2015).

Regarding geographic distribution of scientific productivity and network of authors, institutions, and countries, UK, China, but most of all the USA were largely the most central countries, with University of California, NIH in the USA and UCL in the UK being particularly scientifically productive in this research area. More recently a central role emerged for Canada, with the University Health Network and the Canadian Rapid Treatment Center of Excellence, both in Toronto, having the greatest strength of citations from 2016 to 2021. The emerging interest in Canada for psychedelic research parallels recent legislative and policy changes, that clearly head in the direction of facilitating safe and evidence-based monitored use of psychedelic-assisted psychotherapy (Mocanu et al., 2022). After around 50 years from its criminalization, in 2020 the first exemptions for legal possession of psilocybin were granted in Canada (Therapsil, 2020), and in January 2022 a decision issued in 2013 that banned psilocybin from special access program (SAP) for medical reasons, was reversed (Eggertson, 2013). Similar changes in policy and legal framework around psychedelics are occurring in other countries, yet at a different pace, also accounting for political and cultural differences (Aday et al., 2020; Wang et al., 2017).

Research on psychedelics is increasingly pointing towards combining pharmacological and non-pharmacological interventions. Burstness analysis of the 2020-2022 co-occurrence authors' keywords indicate that among the most cited keywords were 'oral antidepressant', 'default mode network', 'multiple sclerosis', 'psilocybin treatment' and 'cognitive behavioral therapy'. Importantly, psychedelics seem to bridge the classic dichotomy between pharmacological and non-pharmacological interventions, using the effects of the pharmacological intervention as a key to enhance psychotherapy (Eleftheriou and Thomas, 2021; Wolff et al., 2020). The paradigm of conceiving the beneficial effect of psychedelics as intrinsically bound with psychotherapy is evident in the protocol of MDMA-assisted psychotherapy RCTs for PTSD.

Finally, a number of gaps in research trends could be determined, such as genetic susceptibility to the effects of psychedelics (Kim et al., 2020). The biological substrates and key mediators of psychedelics' rapid and sustained antidepressant action remain unknown. De la Fuente Revenga and colleague have recently published a paper on the prolonged epigenomic and synaptic plasticity alterations following single exposure to 2,5-Dimethoxy-4-iodoamphetamine in mice (de la Fuente Revenga et al., 2021).

Other potential gaps are the use of psychedelics for dementia or psychosis, and the testing in pre-clinical models of NPS/NPS-derived novel compounds as future candidates for psychopharmacological treatment of mental disorders, mimicking the transition of psychedelics and dissociative substances from substance of abuse, to powerful treatment options for severe mental disorders.

4.4. Limitations

This work has several limitations, partly due to the nature of scientometric analysis, which rely mostly on co-citations, and do not necessarily indicate the quality of research (Greenberg, 2009). Hence, highly cited or central co-cited references are not necessarily those of highest quality. Another limitation, is the use of only one database, mainly due to the necessity of extraction both full references and citations lists, and the absence of reliable automatic duplicate removal for very large dataset with incomplete Digital Object Identifiers (DOIs) (Visser et al., 2021). Furthermore, produced networks - in particular co-authorship networks - must be interpreted with caution as it is entirely dependent of the extracted dataset, which did not undergo systematic screening. Finally, this scientometric approach does not assess the content of included publications, and so requires clinical and methodological knowledge to interpret findings.

5. Conclusions

This scientometric analysis provides historical insights and perspectives in clinical research on hallucinogens, entactogens, entheogens and dissociative drugs. There is a clear trend towards clinical testing of MDMA, psilocybin, ketamine and its enantiomers, in treatment formats that are frequently associated with psychotherapy, for several mental disorders, in particular PTSD and depression in which evidence syntheses have also been conducted; and also for substance use disorders, anorexia nervosa, and beyond mental disorders for pain and in palliative care in people with cancer. The mechanisms underlying ketamine's efficacy are being explored. NPS are emerging as a public health issue, with the need for toxicology screening in the context of emergency care in particular. The USA and Canada are the countries that are more active in the field of psychedelic research, and this matches local legislation trends.

Role of the funding source

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Contributors

MSa and MSo designed the study and wrote the protocol. MSa managed the literature searches and analyses. MSa and CC undertook the statistical analysis, and MSa wrote the first draft of the manuscript. MSa, MSo, CD, AB, ML, VV, LM, YK, SR, GT, DZ, GG, JR, IH, DD and DC contributed to and have approved the final manuscript.

Declaration of Competing Interest

Gabriella Gobbi, received a grant from Diamond Therapeutics Toronto and she is the inventor of a patent on the use of LSD.

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Muhammad Ishrat Husain has provided consultancy to MindSet Pharma Inc., Psyched Therapeutics Inc., and Wake Network Inc. He was a site principal investigator for clinical trial sponsored by Compass Pathways Ltd.

Danilo De Gregorio is consultant at Diamond Therapeutics Inc., Toronto (ON), Canada.

Marco Solmi has received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka.

Anne Buot, David Castle, Chaomei Chen, Charles Daure, Michel Sabe, Luc Mallet, Michael Ljuslin, Gabriel Thorens, Stephane Rothen, Daniele Zullino, Vincent Verroust and Yasser Khazaal declares no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.09.004.

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