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Review article

Half a century of research on antipsychotics and schizophrenia: A scientometric study of hotspots, nodes, bursts, and trends

Michel Sabe [a,*], Toby Pillinger [b,c,d], Stefan Kaiser [a], Chaomei Chen [e], Heidi Taipale [f,g,h], Antti Tanskanen [f,h], Jari Tiihonen [f,h,i], Stefan Leucht [j], Christoph U. Correll [k,l,m], Marco Solmi [n,o,p]

[a] Division of Adult Psychiatry, Department of Psychiatry, University Hospitals of Geneva, 2, Chemin du Petit-Bel-Air, CH-1226 Thonex, Switzerland
[b] Institute of Psychiatry, Psychology and Neuroscience, Department of Psychosis Studies, King's College of London, London, UK
[c] Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, Imperial College London, London, UK
[d] Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London, UK
[e] College of Computing & Informatics, Drexel University, Philadelphia, PA, USA
[f] Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland
[g] University of Eastern Finland, School of Pharmacy, Kuopio, Finland
[h] Department of Clinical Neuroscience, Karolinska Institutet and Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden
[i] Neuroscience Center, University of Helsinki, Helsinki, Finland
[j] Department of Psychiatry and Psychotherapy, Technical University of Munich, School of Medicine, Munich, Germany
[k] Department of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA
[l] Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA
[m] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany
[n] Department of Psychiatry, University of Ottawa, Ontario, Canada
[o] Department of Mental Health, The Ottawa Hospital, Ontario, Canada
[p] Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program University of Ottawa, Ontario, Ottawa

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ABSTRACT

Changes over 50 years of research on antipsychotics in schizophrenia have occurred. A scientometric synthesis of such changes over time and a measure of researchers' networks and scientific productivity is currently lacking. We searched Web of Science Core Collection from inception until November 5, 2021, using the appropriate key. Our primary objective was to conduct systematic mapping with CiteSpace to show how clusters of keywords have evolved over time and obtain clusters' structure and credibility. Our secondary objective was to measure research network performance (countries, institutions, and authors) using CiteSpace, VOSviewer, and Bibliometrix. We included 32,240 studies published between 1955 and 2021. The co-cited reference network identified 25 clusters with a well-structured network (Q=0.8166) and highly credible clustering (S=0.91). The main trends of research were: 1) antipsychotic efficacy; 2) cognition in schizophrenia; 3) side effects of antipsychotics. Last five years research trends were: 'ultra-resistance schizophrenia' (S=0.925), 'efficacy/dose-response' (S=0.775), 'evidence-synthesis' (S=0.737), 'real-world effectiveness' (S=0.794), 'cannabidiol' (S=0.989), and 'gut microbiome' (S=0.842). These results can inform funding agencies and research groups' future directions.

1. Introduction

Antipsychotic medications are considered the first-line gold standard treatment for schizophrenia (Kahn et al., 2015). First-generation antipsychotics (FGAs) were discovered in the 1950 s, and they possess prevalent dopamine receptor antagonist activity along with histamine and cholinergic receptor antagonism. FGAs were initially developed to treat positive symptoms of psychosis, and they have also been proven to be effective in the treatment of other conditions, such as agitation and acute mania (Correll et al., 2021; Paris et al., 2021; Yildiz et al., 2015).

Abbreviations: WOSCC, Web of Science Core Collection; DSM, Diagnostic and Statistical Manual; ICD, International Statistical Classification of Diseases and Related Health Problems; RCT, Randomized Controlled Trial.

* Corresponding author.
E-mail address: michel.sabe@hcuge.ch (M. Sabe).

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FGAs are associated with a high rate of side effects, such as extrapyramidal side effects, including rigidity, bradykinesia, dystonia, tremor, akathisia, tardive dyskinesia (Carbon et al., 2018; Huhn et al., 2019; Rummel-Kluge et al., 2012), and hyperprolactinemia (Taipale et al., 2021). Second-generation antipsychotics (SGAs) were introduced in the 1980 s and are dopamine-serotonin antagonists, mainly because of their high affinity for 5-HT2A receptors (Correll, 2010). SGAs gained popularity over FGAs thanks to a lower risk of neurological and cognitive side effects; however, specific side effects of SGAs were also uncovered, including cardiometabolic side effects such as weight gain, hyperglycemia, and dyslipidemia (Galling et al., 2016; Pillinger et al., 2020). More recently, "third-generation" antipsychotics (TGAs) have been developed. They mostly act as serotonin-dopamine activity modulators (partial agonists), overall with fewer side effects than FGAs and SGAs (Amato et al., 2018; Kishi et al., 2020; Sabe et al., 2021).

Over the years, systematic reviews, meta-analyses, umbrella reviews, and practice guidelines have offered a deep synthesis of specific research questions in psychiatry, and hundreds of publications have discussed the topic of antipsychotics for patients with schizophrenia (Galderisi et al., 2021; Lobo et al., 2022; Radua et al., 2012; Solmi et al., 2020).

Such a significant growth in the literature requires new approaches to review and analyze trends within knowledge domains (Chen, 2006a; van Eck and Waltman, 2010). Nakagawa and colleagues recently proposed a new framework for research synthesis of both evidence and influence, named research weaving (Nakagawa et al., 2019). This framework combines systematic mapping and bibliometric analysis to inform the development of a field, the influence of research papers and their interconnections, and to visualize content across and within publications. Systematic mapping allows one to visualize and map the evolution of research over time, while bibliometric analyses measure how evidence is interconnected and the influence of authors via two different methods, namely performance analysis and bibliometric mapping (Nakagawa et al., 2019). This combination of systematic mapping and bibliometric analyses, that can be defined scientometric analysis, by providing a broad synthesis of a research field and how it has changed over time not only helps researchers and clinicians to have a clearer overview of the research on a given topic but also, can identify research abundancies, gaps, and trends, as well as visualization of potential moderators (e.g., publication year and methodological differences), bias, or limitations. Scientometric analyses can be relevant in psychiatry, and in psychopharmacology in particular, given the notable changes in profile of available medications, their efficacy, effectiveness, safety, and the evolution of sources of evidence on antipsychotics for the treatment of schizophrenia. Although bibliometric studies examining publication trends in the field of antipsychotics and schizophrenia have previously been published for individual countries, to our knowledge, no scientometric study has been conducted to date.

Given the aforementioned, we have conducted a scientometric study combining bibliometric analyses and systematic mapping on the topic of antipsychotics for patients with schizophrenia and related disorders.

2. Methods

2.1. Objectives

Our primary objective was to produce systematic mapping of how research on antipsychotics for patients with schizophrenia and related disorders has evolved over time and identify the evolution of key research themes by using networks of co-cited references and networks of co-occurring keywords.

Our secondary objective was to provide clinicians and researchers with a measure of the research network (countries, institutions, authors, and journals) and to detect research abundancies, gaps, emerging trends, biases, and limitations.

2.2. Search strategy and data collection

We searched the Web of Science Core Collection (WOSCC) as the most comprehensive database for scientometric analyses (Mongeon and Paul-Hus, 2016). Our search terms combined Medical Subject Headings words and keywords such as 'schizophrenia' and 'antipsychotic* '. The full search terms are available in the study protocol (Supplementary information 1). The database source was limited to Science Citation Index Expanded, publication types to 'article' or 'review', with no limitation of language/time. The full records with cited references published until November 5, 2021, were extracted form WOSCC into in tag-delimited plain text files. Duplicates were eliminated with CiteSpace.

We conducted the extraction and reported the reason for the exclusion of articles in the flowchart (Supplementary Fig. 1).

2.3. Data analysis

We used the Bibliometrix R packages (3.1.4)(Aria and Cuccurullo, 2017), VOSviewer (1.6.16)(van Eck and Waltman, 2010), and CiteSpace (5.8. R3)(Chen, 2006b) to conduct the analyses. Units of measure were author, journal, reference, country, institution, and keyword.

Networks used in science mapping include directed and undirected graphs. Direct citation networks are directed graphs, whereas co-citation and co-occurrence networks are undirected graphs. A comparative study of direct citation and co-citation networks can be found in (Boyack and Klavans, 2010). Bibliometric outcomes included citation counts, co-citations and co-occurrences (Boyack and Klavans, 2010). Citation count are the number of citations to a publication, and co-citation count is defined as the frequency with which two published articles are cited together by subsequently published articles (Small, 1973). A co-citation network is particularly suitable for systematic reviews because co-citation linkages may reveal how groupings continuously evolve independently from original publications. Co-occurrence networks are a graphical representation of how frequently variables appear together. Systematic mapping outcomes were networks and co-citations (or co-occurrence) clusters. The interpretation of these clusters is augmented by CiteSpace's automatic cluster labeling and summarization (Chen et al., 2010).

CiteSpace produces a variety of metrics of significance, with temporal metrics such as citation burstness, structural metrics such as betweenness centrality, modularity, and silhouette score as well as a combination of both, namely, the sigma metric. Betweenness centrality measures the number of times a node (e.g., one article, one author) lies on the shortest path between other nodes based on Freeman's betweenness centrality metric (Freeman, 1977). Nodes with high betweenness centrality generally connect different clusters and are considered key hubs. Burstness measures the rate of change. The burstness of the frequency of an entity over time indicates a specific duration when an abrupt change in the frequency takes place, thus identifying emergent terms (Kleinberg, 2003). CiteSpace also combines betweenness centrality as a structural property with citation burstness as a temporal property using a metric called sigma. Sigma is computed as $(\text{centrality} + 1)^{\text{burstness}}$ (Chen et al., 2010) with higher values indicating works with higher influential potential. The modularity (the Q score) of a network measures the extent to which a network can be divided into modules or clusters, and the silhouette (the S score) is a method of interpretation and validation of consistency within clusters of data (Shibata et al., 2008). The Q metric ranges from 0 to + 1, and the S metric ranges from − 1 to + 1. For both metrics, a score close to + 1 represents the best clustering model. When the Q value is 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. A silhouette score of 1 may, however, indicate that the corresponding cluster is relatively isolated.

The cluster labels are generated from noun phrases of the keyword lists of articles cited in each cluster using the likelihood ratio test ($p < 0.001$). Each cluster was closely inspected, and automatic labels were re-labelled according to authors' expertise, if needed.

When examining the burstness of published articles, which indicates that a particular article is associated with a surge of citations, we excluded from the model the reference referring to describing and classifying mental disorders (e.g., DSM, ICD-10). Where appropriate, we merged redundant nodes (e.g., nodes for the author Kane J and Kane JM). The impact factors of the included journals were retrieved from the 2021 Journal Citation Reports (data were extracted from WOSCC in plain text files).

The Bibliometrix R package was used with R version 4.0.5 to obtain the main information on authors and journals. VOSviewer (version 1.6.17) was used to obtain network maps of most-cited journals and co-occurring author keywords networks. CiteSpace (version 5.8. R3) was used for the extraction of collaboration networks (across countries and institutions), co-citation analysis (co-cited authors, co-cited reference cluster), and co-occurrence analysis (co-occurring author keywords networks). Burst analyses were conducted with CiteSpace for all units of measure. The g-index, an author-level metric based on the distribution of citations received that alleviates bias from highly cited papers as seen with the h-index, was used for all calculations (Egghe, 2006). Of importance, the inflated values of the g-Index help to give credit to lowly-cited or non-cited papers while giving credit for highly-cited papers, making g-index most relevant for co-cited analysis. CiteSpace also reduces the timeframe by removing empty time intervals to optimize time slicing. CiteSpace parameters can be found in Supplementary information 2 and Supplementary Fig. 1. The scale factor k was set to 25 for all analysis.

3. Results

3.1. Analysis of co-cited reference: clusters of research and most cited papers

3.1.1. Clusters of research

We generated a map of reference co-citations with corresponding clusters that permits the extraction of landmark references and clusters of research (Fig. 1A.B). The first identified article was published in 1955, however, the time slicing from 1955 to 2021 was reduced to 1980–2021 by the software CiteSpace to fit the slicing process by removing empty time intervals.

We identified 25 different clusters in this network of co-citation

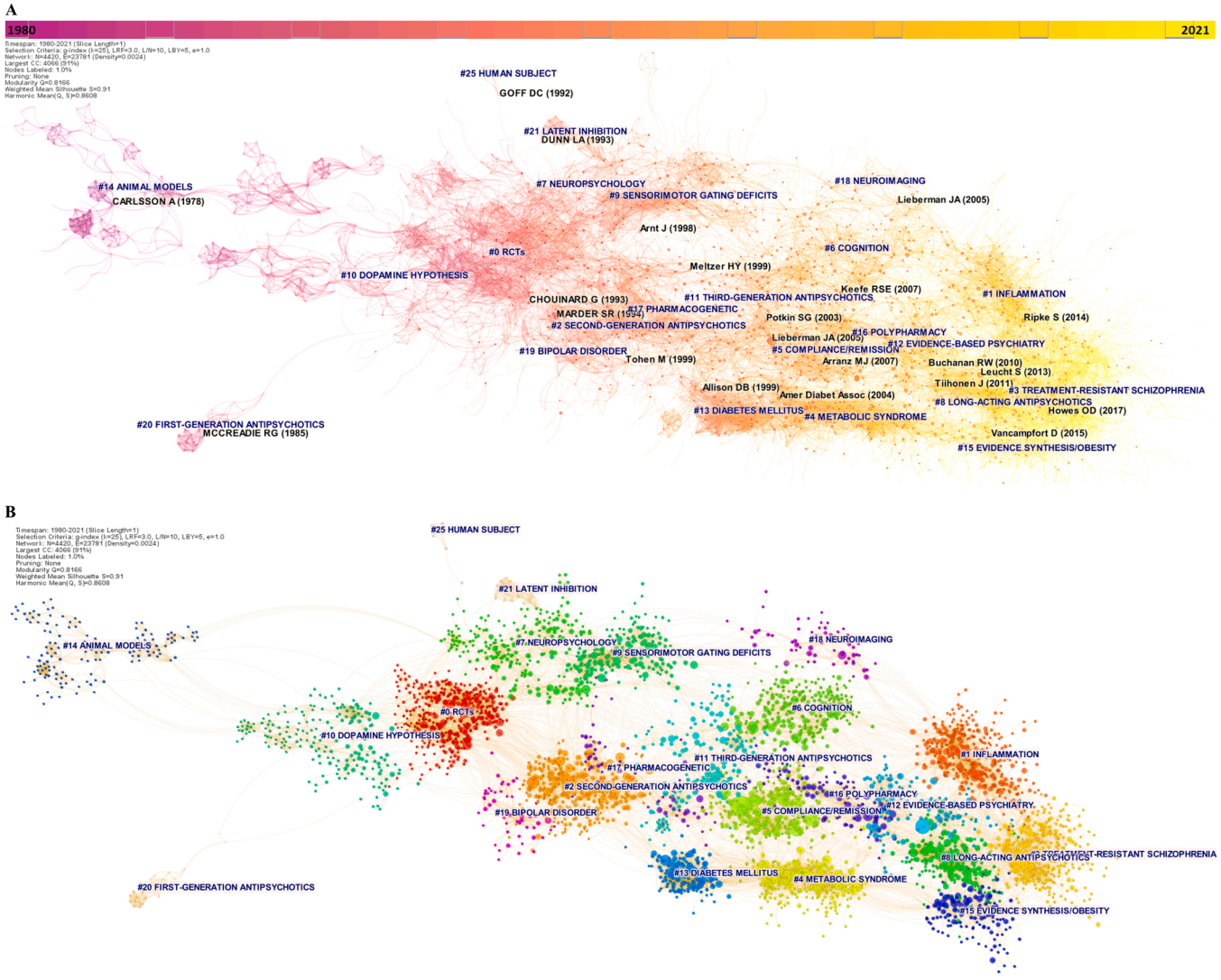

Fig. 1. Co-citation references network (1980–2021) and correspondent clustering analysis obtained with CiteSpace. *Note: (A) Co-citation reference network with cluster visualization and burstness of hotspots. The size of a node (article) is proportional to the number of times the article has been co-cited. Burstness is represented by red tree rings, with either important citation burst. (B) Visualization map of the corresponding clusters.*

references with significant modularity and silhouette scores indicating highly credible clusters (Q=0.8166; S=0.91). Details of the extracted clusters are available in Supplementary Fig. 2 and Supplementary Table 1.

Three different major trends of research regrouped in a single constellation were found. The first and most important trend concerned antipsychotic efficacy and started in 1980–1990 with two research clusters. These clusters, with indication of the label, size, silhouette score, the average year of publication of the cluster members and most representative reference were: clusters #14 ('animal models';142; S=0.995; 1979)(Carlsson, 1978) and #20 ('first-generation antipsychotics'; 22; S=0.997; 1986)(McCreadie et al., 1985). These clusters shared hotspots with cluster #10 ('dopamine hypothesis'; 193; S=0.888; 1990)(Davis et al., 1991), which further evolved into clusters #0 ('RCT'; 388; S=0.837; 1993)(Chouinard et al., 1993), #2 ('second-generation antipsychotics'; 306; S=0.874; 1997)(Marder and Meibach, 1994) and #11 ('third-generation antipsychotics'; 173; S=0.899; 2002)(Potkin et al., 2003). This single research trend describes the evolution from research on first-, to second- and third-generation antipsychotics, which further branch into 6 different clusters: #5 ('compliance/remission'; 251; S=0.911; 2004)(Lieberman et al., 2005), #16 ('polypharmacy'; 115; S=0.936; 2007)(Buchanan et al., 2010), #12 ('evidence-based psychiatry'; 155; S=0.936; 2011)(Leucht et al., 2013), #8 ('long-acting antipsychotics'; 233; S=0.926; 2013)(Tiihonen et al., 2011) and #3 ('treatment-resistant schizophrenia'; 306; S=0.877; 2016)(Howes et al., 2017) (Supplementary Table 1).

The second major trend of research concerns cognition in schizophrenia. It starts with research on nicotine with cluster #25 ('nicotine'; 6; S=0.998; 1993)(Goff et al., 1992), which develops research on the cognitive deficit with cluster #21 ('latent inhibition'; 21; S=0.998; 1994)(Gray et al., 1995), #7 ('neuropsychology'; 235; S=0.882; 1993) (Meltzer and McGurk, 1999) and #9 ('sensorimotor gating deficits'; 202; S=0.928; 1998)(Arnt and Skarsfeldt, 1998). More recently, these clusters became cluster #6 ('cognition'; 238; S=0.872; 2005)(Keefe et al., 2007), with strong links to cluster #11 third-generation antipsychotics that have fewer impacts on cognitive functioning than less recent antipsychotics.

The third major research trend concerns the side effects of antipsychotics. These trends begin in 2000, with the first cluster on antipsychotic-induced weight gain, cluster #13 ('diabetes mellitus'; 144; S=0.946; 2000)(Allison et al., 1999), which evolved into cluster #4 ('metabolic syndrome'; 279; S=0.867; 2007)(ADA, 2004) and has currently evolved into cluster #15 with evidence synthesis and prediction of risks ('evidence synthesis/obesity'; 137; S=0.928; 2015)

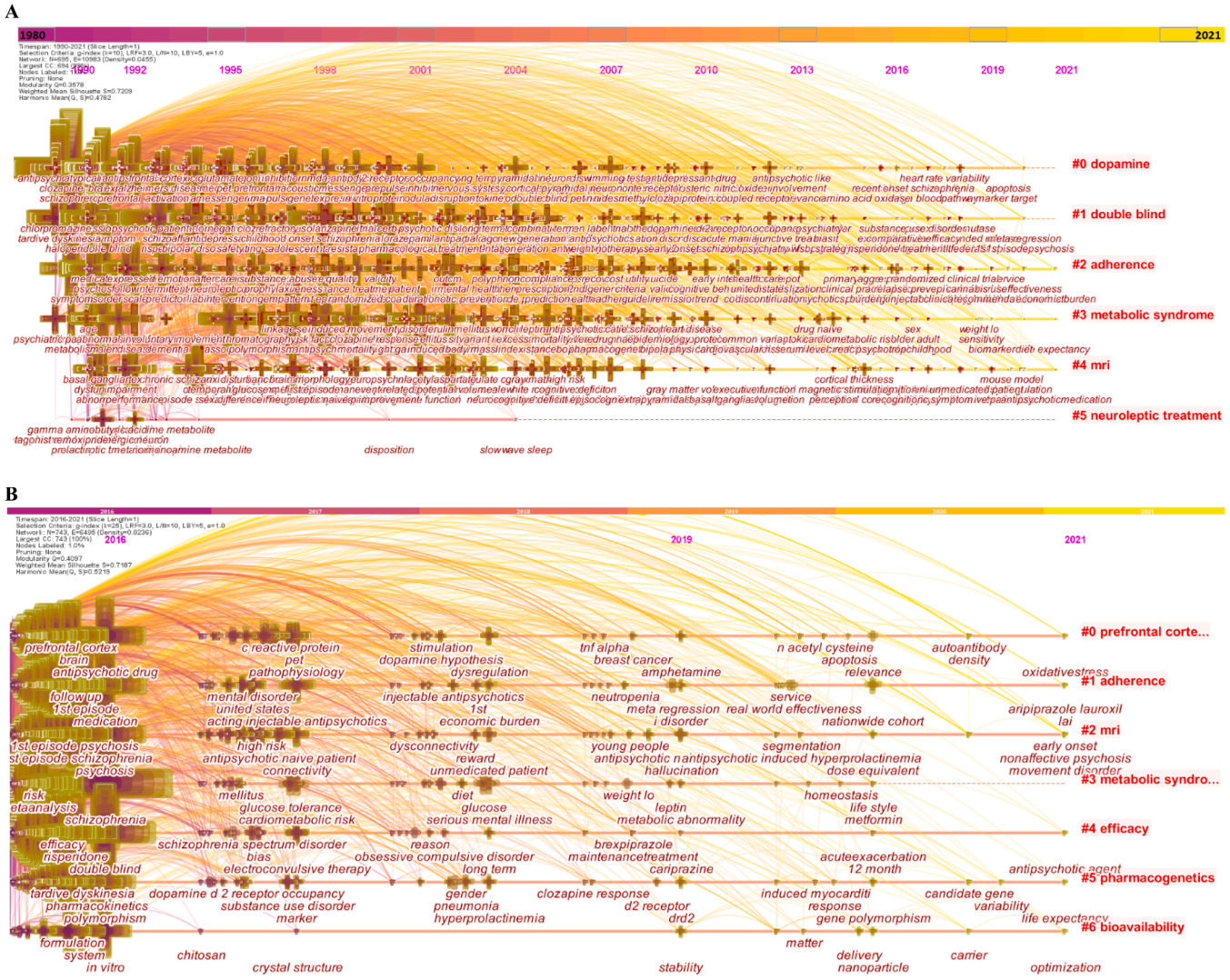

Fig. 2. Timeline visualization of co-occurring author keywords networks ((A) 1980–2021 and (B) 2016–2021). *Note: The nodes represent keywords, and the colors show the average year of publication for each node. The size of a cross is proportional to the burstness of keyword co-occurrence. The co-occurrence network is weighted on total link strength across different keyword nodes and scored on the average publication years. The clusters are labeled in red at the far right of the timeline maps.*

(Vancampfort et al., 2015).

Furthermore, three relatively independent trends of research were also found: one on antipsychotics for bipolar disorders #19 ('bipolar disorder'; 52; S=0.985; 1995)(Tohen et al., 1999), one on genetics #17 ('pharmacogenetics'; 71; S=0.957; 2000)(Arranz and de Leon, 2007), and one on inflammation #1 ('inflammation'; 336; S=0.889; 2012)

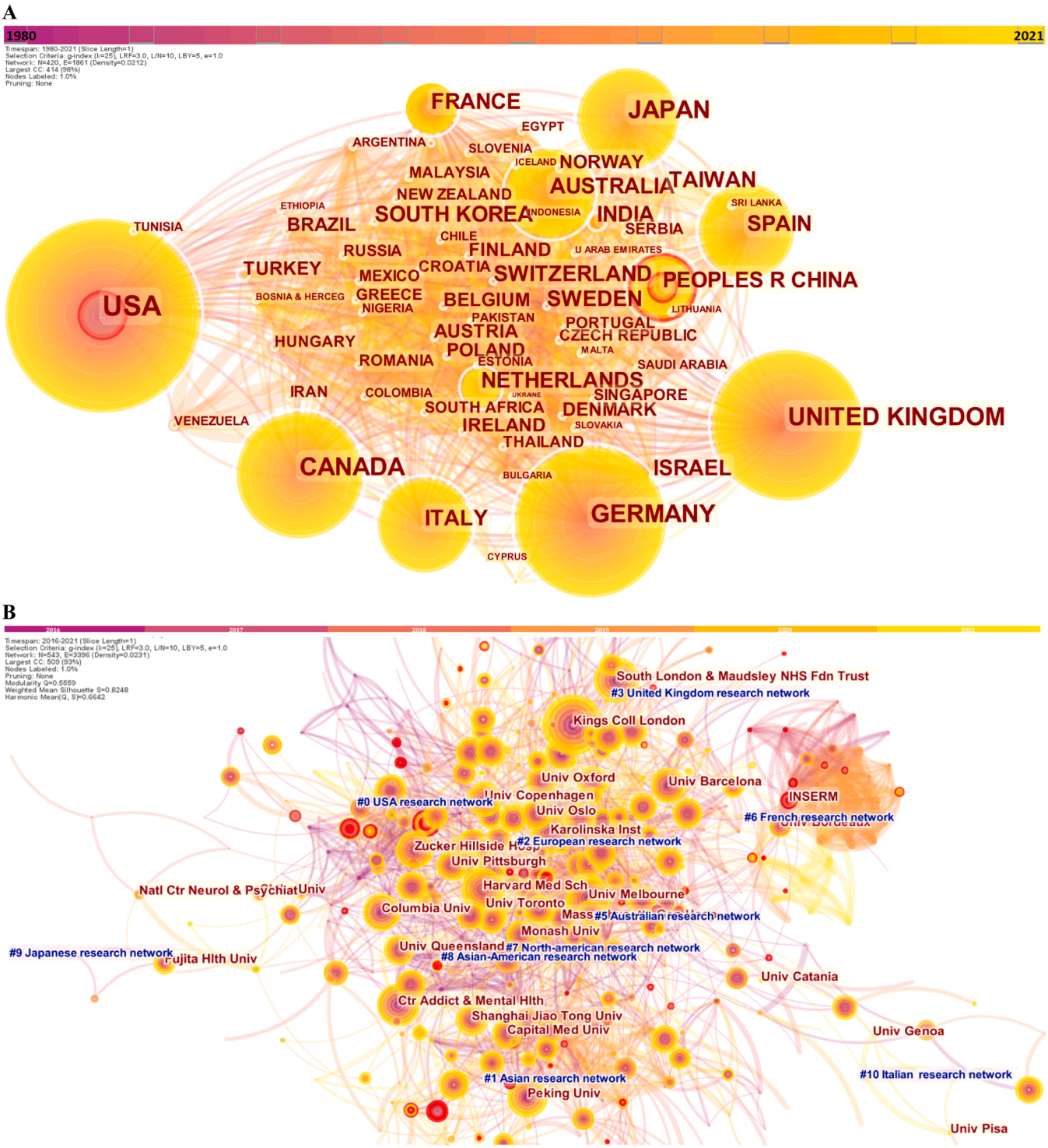

Fig. 3. Network of the co-authors' countries (A) and the network of co-authors institutions (B)(C) for antipsychotics for schizophrenia from 1980 to 2021 obtained with CiteSpace. *Note:* (A) The visualization map of the collaborative country network (based on co-authors' countries) reveals the influence of each node. The network is organized by betweenness centrality, and centrality scores are normalized to the unit interval of [0,1]. A node of high betweenness centrality is usually one that connects two or more large groups of nodes. A node with a strong betweenness centrality score has a great influence on a network. High betweenness centrality is represented by the thickness of a purple trim. The nodes were limited to the top 50 countries. Burstness of citation is revealed with the presence of red tree rings. The thicker the red tree rings, the more burstness for the corresponding node. (B) Visualization map of the network of co-author institutions, according to the degree of citations. Annual citations of each institution are rendered as citation tree rings. The most recent citations correspond to the innermost rings. Nodes with outermost rings in purple are identified as hotspots. The color of a link represents the earliest time slice in which the connection was first made. (C) Network of co-author institutions with representation of identified clusters.

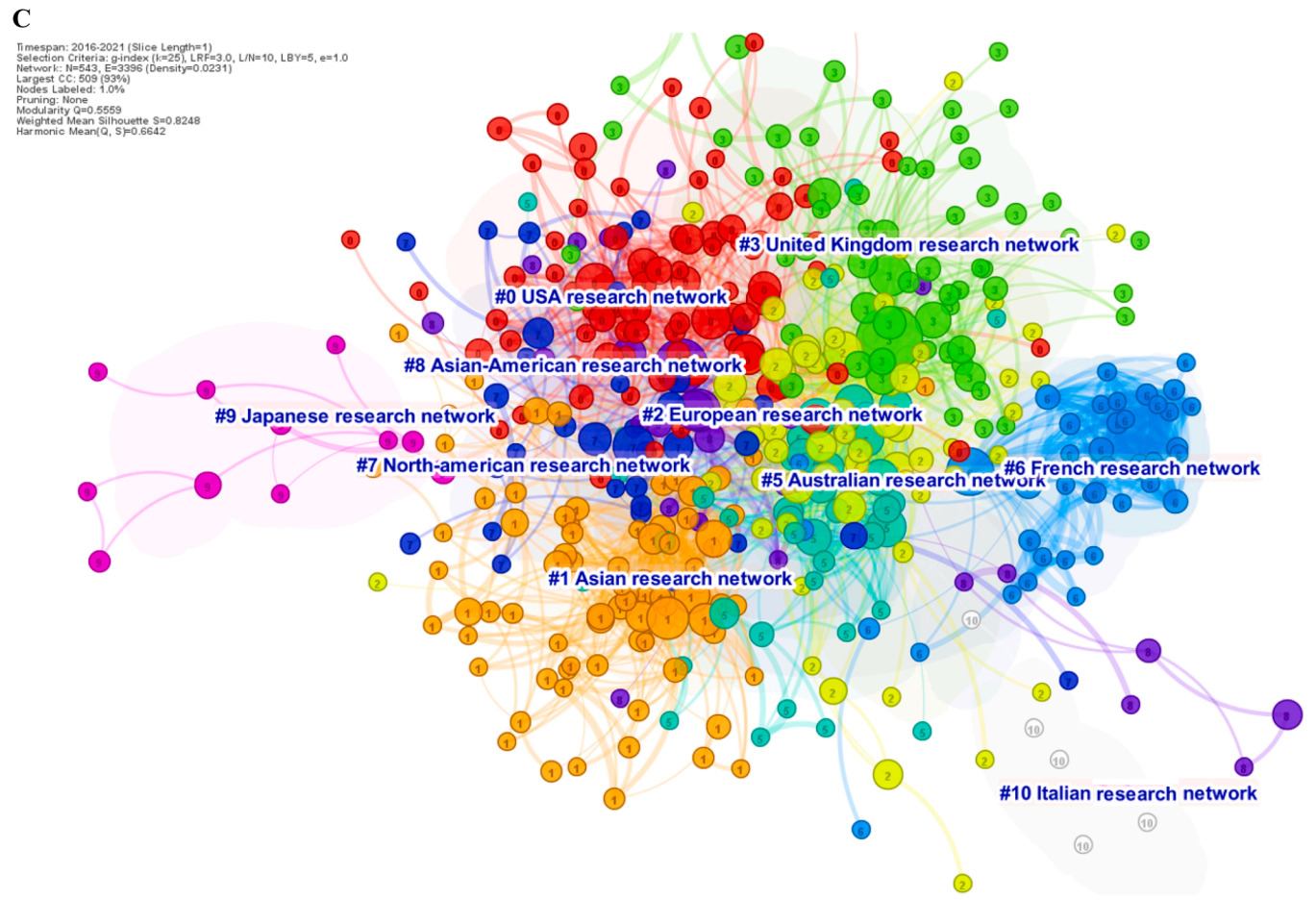

Fig. 3. (*continued*).

(Miller et al., 2011), which is linked to clusters #6 and #18.

The link walkthrough over time between clusters based on burstness dynamics for this co-cited reference network (1980–2021) is available in the supplement Fig. 3 and as a video on osf.io (https://osf.io/qkybf/?view_only=3c251cbd3e4f47908366aa7f7f45d2e3).

To further examine research trends, we focused on the last five years co-citations reference network (2016–2021) and on each month of the last available year (2021) (Supplementary Figs. 4–6). For both networks, the modularity score was significant, and the silhouette suggested highly credible clusters (Q=0.6912; S=0.8774 and Q=0.536; S=0.8186, respectively). The two corresponding networks reveal the latest evolution of three major research trends that were previously identified: 'treatment-resistant schizophrenia' (Fig. 1) became a cluster with numerous neuroimaging studies #3 ('glutamate'; 95; S=0.822; 2016) (Howes et al., 2015) (Supplementary Fig. 4), and in 2021, that further evolved into cluster #7 ('ultra-treatment resistance'; 65; S=0.925; 2017)(Campana et al., 2021) and #5 ('efficacy/dose–response'; 81; S=0.925; 2017)(Galling et al., 2017). The 'long-acting injectable' became cluster #2 ('real-world evidence'; 111; S=0.923; 2014)(Tiihonen et al., 2017); 'inflammation' then became cluster #11 ('pharmacogenetics'; 5; S=0.997; 2017)(Mauri et al., 2014), cluster #10 ('cannabidiol'; 9; S=0.989; 2016)(McGuire et al., 2018), and #4 ('cytokines/pharmacokinetic'; 93; S=0.916; 2018)(Goldsmith et al., 2016) and cluster #6 in 2021 ('gut microbiome'; 75; S=0.842; 2017) (Penninx and Lange, 2018).

Finally, in 2021, an entirely new emerging cluster on lipid biosynthesis and transdermal drug delivery cluster was detected #11 ('lipid biosynthesis/transdermal drug delivery'; 5; S=0.993; 2018)(Iwata et al., 2020) (Supplementary Fig. 6).

3.1.2. Most cited papers and turning-point papers

We report the top 10 most co-cited references in Table 1. The randomized controlled trial (RCT) published by Lieberman et al., 2005 in the New England Journal of Medicine (Lieberman et al., 2005) was the most co-cited paper, with 1091 citations in our network and 6657 citations in the literature. The second- and third-most cited papers are two meta-analyses on the comparative efficacy and tolerability of antipsychotics in schizophrenia published by Leucht et al., (2009, 2013) in The Lancet (Leucht et al., 2013, 2009), with 546 and 466 citations in our network, compared with 2213 and 2171 citations in the literature, respectively. We also extracted the top 25 most co-cited papers from the last 5 years (Supplementary Table 2.U.). Leucht et al.'s 2013 meta-analysis is now the most cited paper, followed by the guidelines on treatment-resistant patients by Howes et al., 2017 (Howes et al., 2017) and the Schizophrenia Working Group of the Psychiatric Genomics Consortium case–control study on schizophrenia-associated genetic loci (Ripke et al., 2014).

In addition, the analysis of burstness revealed that the top 3 references with the strongest beginning of citation burst were 3 RCTs (Chouinard et al., 1993; Marder and Meibach, 1994; Tollefson et al., 1997) (Supplementary Table 2.S.T). When focusing on the last 5 years, the corresponding citations were Leucht and colleagues' meta-analysis on antipsychotics (Leucht et al., 2013), the cohort study on depot antipsychotics by Tiihonen et al., 2011 (Tiihonen et al., 2011) and the guidelines for biological treatment of schizophrenia by Hasan et al., 2012 (Hasan et al., 2012), thus underpinning the importance of evidence synthesis over individual RCTs in the last decade (Supplementary Table 2.U.V).

In addition, we identified intellectual 'turning-point' papers, which

Table 1
The top 10 most cited references.

Top 10 co-cited references										
Number of citations in the network	Number of citations in the literature[a]	Cited reference	Year	Source	Vol	Page	Title	Doi	Type of paper	Related cluster in Fig. 1
1091	6657	Lieberman JA	2005	NEW ENGL J MED	353	1209	Effectiveness of antipsychotic drugs in patients with Chronic Schizophrenia	10.1056/NEJMoa051688	RCT	5
546	2213	Leucht S	2013	LANCET	382	951	Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis	10.1016/S0140–6736(13)60733–3	Meta-analysis	8, 3
466	2171	Leucht S	2009	LANCET	373	31	Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis	10.1016/S0140–6736(08)61764-X	Meta-analysis	5, 8, 16
301	1271	Kahn RS	2008	LANCET	371	1085	Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial	10.1016/S0140–6736(08)60486–9	RCT	5
295	1433	Jones PB	2006	ARCH GEN PSYCHIAT	63	1079	Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)	10.1001/archpsyc.63.10.1079	RCT	16
292	1729	Marder SR	1994	Am J Psychiat	151	825–835	Risperidone in the treatment of schizophrenia.	10.1176/ajp.151.6.825	RCT	2
2822	1196	Tollefson GD	1997	AM J PSYCHIAT	154	457	Olanzapine Versus Haloperidol in the Treatment of Schizophrenia and Schizoaffective and Schizophreniform Disorders: Results of an International Collaborative Trial	10.1176/ajp.154.4.457	RCT	2
282	3221	Allison DB	1999	AM J PSYCHIAT	156	1686–96	Antipsychotic-induced weight gain: a comprehensive research synthesis.	10.1176/ajp.156.11.1686.	Review	13
277	1409	Davis JM	2003	ARCH GEN PSYCHIAT	60	553	A meta-analysis of the efficacy of second-generation antipsychotics	10.1001/archpsyc.60.6.553	Meta-analysis	5
276	2541	Amer Diabet Assoc	2004	Diabetes Care	27	596–601	Consensus development conference on antipsychotic drugs and obesity and diabetes.	10.2337/diacare.27.2.596.	Guideline	4, 13

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

are papers associated with significant contributions as a domain advance, such as: the Marder and colleague paper, central to cluster #2 ('second-generation antipsychotics')(Marder and Meibach, 1994) that was used in the FDA approval of risperidone in 1993; the Tollefson and colleagues paper, central to cluster #2 (Tollefson et al., 1997) that was used for the FDA approval of olanzapine in 2004; the Leucht and colleague meta-analysis, in cluster #5(medication adherence')(Leucht et al., 2009), essential to clinicians and evidence-synthesis, that further develops cluster #12 ('evidence-based psychiatry') with an updated version of this work (Leucht et al., 2013); and finally the Howes et al. (2017) guideline paper on treatment response and resistance in Psychosis, is paramount to understand cluster #3 ('treatment-resistance schizophrenia')(Howes et al., 2017).

3.2. Co-occurring author keywords networks

Research hotspots and trends of research were examined by analyzing the most cited keywords.

We extracted the timeline of the co-occurring authors' keyword network (1980–2021) using CiteSpace (Fig. 2A). Six clusters of keywords were identified, and the most important was 'dopamine', followed by 'double blind', 'adherence', 'metabolic syndrome', 'MRI', and 'neuroleptic treatment'. We further extracted the same network while focusing on the 2016–2021 period (Fig. 2B), and seven clusters were identified. The most important cluster was 'prefrontal cortex', followed by 'adherence', 'MRI', 'metabolic syndrome', 'efficacy', 'pharmacogenetics', and 'bioavailability'. Both co-occurring author keywords networks (1980–2021 and 2016–2021) presented a significant silhouette score ($S>0.6$) and an acceptable modularity score ($Q>0.3$).

Moreover, the results for burstness revealed that the three most cited keywords ranked by the beginning of citation bursts were 'haloperidol' (1990), 'neuroleptics' (1990), and 'tardive dyskinesia' (1990) (Supplementary Table 2.Y.Z). When considering the 2016–2021 time period, the keywords with the latest beginning of citation burst revealed the latest keyword trends, which were 'nationwide cohort', 'target', 'nanoparticle', and 'real-world effectiveness'. In addition, the 2021 keywords with the strongest strength of citation bursts were 'relapse', 'gene expression', and 'discontinuation'.

We further extracted the overlay of visualization for the co-occurring author keywords networks based on the average publication years (2000–2021 time period) with VOSviewer (Supplementary Fig. 7). Some of the most cited keywords reflecting the latest trends of research were 'inflammation', 'cannabidiol', 'remission', and 'China'.

3.3. Publication outputs and major journals

Our dataset originally contained 39,024 references. Following the data filtering process detailed in our protocol, 17% of the total references were excluded (Supplementary Fig. 1, and supplementary Information 1). Of importance, all the 155 highly cited articles identified by WOSCC were inspected, and all articles were considered are relevant.

The final dataset consisted in 32,240 studies (26,571 articles and 4833 reviews) in 16 different languages published between 1955 and 2022, with an average of 2.17 authors per publication in 1911 different sources (e.g., journals, books). The average number of co-authors per document grew from 3.5 in 1955–1990–4.6 in 1990–2000 and 5.7 in 2000–2021.

The first article identified was a case–control study by Cowden and colleagues on reserpine in the treatment of schizophrenia (Cowden et al., 1955).

The annual scientific production started to increase, particularly since 1990, with an average annual growth rate of 18.7%, continuing to exponentially increase from 224 publications per year in 1990 to a peak of 1459 articles in 2015 and of 1438 articles per year until 2020. The average citations per document per year increased from 1 in 1990–3.8 in 2020 (Supplementary Fig. 8).

The 5 journals with the most references were Schizophrenia Research (n = 1829), The Journal of Clinical Psychiatry (n = 1066), Psychopharmacology (n = 770), Psychiatry Research (n = 743), and The Journal of Clinical Psychopharmacology (n = 682) (Supplementary Fig. 9). The co-cited journal network and the journals with the most publications over the past 20 years are shown in Supplementary Fig. 10. The American Journal of Psychiatry, Archives of General Psychiatry (renamed JAMA Psychiatry in 2013), Schizophrenia Research, Schizophrenia Bulletin, and the Journal of Clinical Psychiatry were the 5 journals that received the highest number of citations (Table 2).

3.4. Analysis of cooperation networks across countries and institutions

The most cited countries and institutions are reported in Supplementary Table 3, and Fig. 3A.B.C.

A total of 87 countries were identified. The United States of America (USA) presented an all-time central place with the highest degree of centrality (175), followed by the United Kingdom (UK) (102) and France (88). Our database revealed that the USA was the most cited country (n = 10,987), followed by the UK, Germany, Canada, Japan, and the Republic of China, which obtained 56% (n = 975) of their total citations in the last 5 years alone.

We identified 1436 different organizations. The top 5 institutions by citation counts were King's College London with 892 citations, followed by the University of Toronto (n = 858), Harvard University (n = 545), Eli Lilly & Co (n = 453), and the Centre for addictions and mental health of the University of Toronto (n = 443). The top 5 institutions/affiliations with the most centrality were Duke University, the University of California Los Angeles, the Zucker Hillside Hospital, Yale University, and the National Institute of Mental Health.

When restricting the timeframe to the last 5 years (2016–2021), the top 5 most cited countries were unchanged, except the People's Republic of China moved ahead of the UK (Supplementary Table 3). In addition, the top 5 most cited institutions were similar, except the University of Melbourne moved ahead of Eli Lilly & Co. We extracted the collaborative institution network (2016–2021) that yielded significant modularity and silhouette scores (Q=0.5559; S=0.8248). This visualization map permits us to observe the influence and burstness of the most important institutions with major hotspots (Fig. 3B.C).

The analysis of burstness revealed that the People's Republic of China had the strongest citation burst strength at all times (173.49); this burst occurred in the last 10 years (Supplementary Table 2.A.B.).

The burst detection analysis also revealed that the NIMH presented the longest citation burst (1981–2004), and Harvard Medical School presented the most recent and the strongest citation burst (2016–2021) (Supplementary Table 2.C.D).

3.5. Analysis of co-authorship network

We retrieved from our database the authors that published the greatest number of papers related to antipsychotics in schizophrenia and the authors' collaborative network (those that participated as co-authors of publications) (Fig. 4 and Supplementary Table 3).

Co-authorship networks permit visualization of the scientific collaboration between authors by using the frequency of co-authorship. The co-authorship network showed significant modularity, and the silhouette score indicated highly credible clusters (M=0.7895; S=0.9285) (Fig. 4A.B.). This network revealed that the most important recent cluster is cluster #1, labeled 'second-generation antipsychotics', based on the likelihood ratio algorithm of keywords, which mainly refers to the most recently developed antipsychotics and long-acting injections (Supplementary Table 4). Lieberman JA and Meltzer HY were identified as two key authors that linked clusters #0 (long-acting antipsychotics) and #1 (second-generation antipsychotics) (Supplementary Fig. 11). The top 5 co-authors with the strongest citation burst in the last 5 years were Correll CU, Maccabe JH, Xianf Y, Zhao J, and Gaughran F (Supplementary Table 2.K.L).

In addition, we conducted the co-authorship network with VOSviewer, revealing a similar network (Supplementary Fig. 12). We further explore citations using the author co-citation network as 'who cites who?' from 2016 to 2021 in our database (Supplementary Fig. 13.A.B.C, Supplementary Table 5). The top 5 co-cited first authors in the 5 years were Correll CU, Vancampfort D, Owen M, Van Erp T and Kane JM; the top 5 co-cited last authors were Sawa A, Correll CU, McCutcheon R,

Table 2
The top 10 most cited journals.

Top journals						
Journals with most articles (1980–2021)	Initial year	Impact factor (2019–2020)	Total articles (%)	Total articles	Journals with most citations (1980–2021)	Total citations
1. Schizophrenia Research	1988	4.93	5,7	1830	1. American Journal of Psychiatry	22,691
2. Journal of Clinical Psychiatry	1978	4.2	3,3	1067	2. Archives of General Psychiatry/JAMA Psychiatry	22,644
3. Psychopharmacology	1959	4.53	2,4	776	3. Schizophrenia Research	19,284
4. Psychiatry Research	1979	3.22	2,3	743	4. Schizophrenia Bulletin	17,157
5. Journal of Clinical Psychopharmacology	1981	2.7	2,1	682	5. Journal of Clinical Psychiatry	16,766
6. Progress in Neuropsychopharmacology	1998	4.8	2,1	670	6. Biological Psychiatry	15,236
7. Schizophrenia Bulletin	1973	7.95	1,9	618	7. British Journal of Psychiatry	15,029
7. Biological Psychiatry	1959	13.38	1,7	547	8. Psychopharmacology	12,301
9. American Journal of Psychiatry	1945	14.12	1,7	541	9. Neuropsychopharmacology	12,034
10. Neuropsychopharmacology	1987	7.8	1,6	511	10. Acta Psychiatrica Scandinavica	11,259

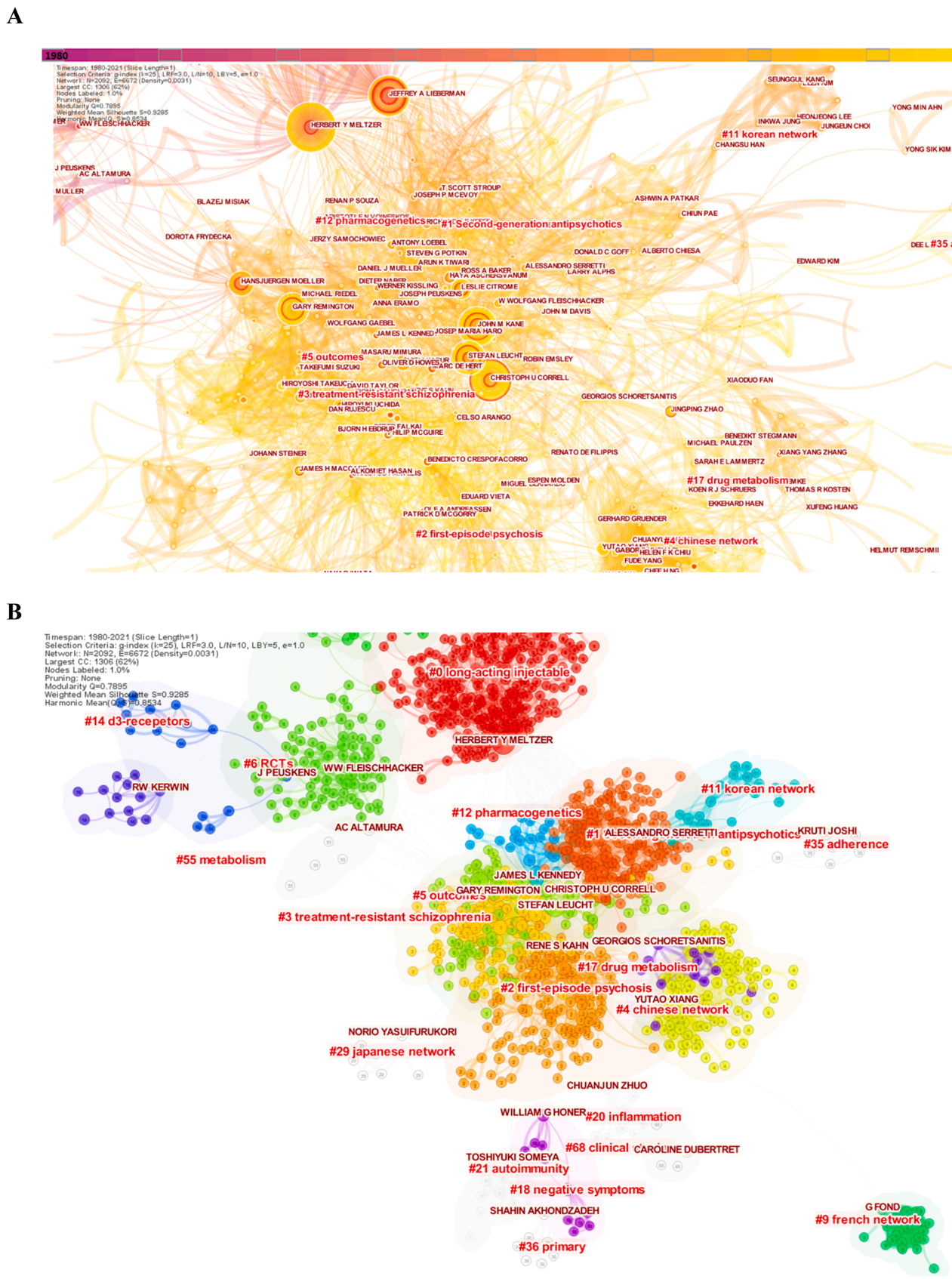

Fig. 4. Co-authorship network (A) with corresponding clusters (B) from 1980 to 2021. *Note:* Co-authorship networks permit visualization of the scientific collaboration between authors based on the frequency of co-authorship. A node represents one author. The links between each author represent collaboration (co-authorship). Both node and link colors indicate the year of the first collaboration (from pink-1980 to yellow-2021). The size of the node is proportional to the number of co-authorships of the author.

Solmi M and Hibar DP (Supplementary Table 3); the top 3 authors with the highest sigma score, combining betweenness centrality and burstness, were Correll CU, Kane JM and Leucht S.

Furthermore, in the last 5 years, the top 3 authors with the strongest citation bursts were Leucht S, Howes OD, and Correll CU (Supplementary Table 2. P).

4. Discussion

4.1. Summary of the main findings

Three different software packages were employed to present a comprehensive overview of the development of antipsychotic drug research over the last 60 years (CiteSpace and VOSviewer with the 1980–2022 time period, Bibliometrix R package with 1955–2021 time period), with leading countries, institutions, authors, journals, hotspots, and trends in research for antipsychotics in schizophrenia characterized.

We identified an exponential growth of publications on antipsychotics in schizophrenia since 1990, and as of 2010, a steady average number of more than 1400 articles published per year. The USA was the country with the most total publications and citation count, followed by the UK. Over the last 10 years, China presented a relevant growth of publications and citation burst that permitted China to advance ahead of the UK. King's College London was the most cited and productive institution at all times. The top 5 most productive and cited authors were Meltzer HY, Lieberman JA, Kane JM, Correll CU and Remington G; the top 5 authors with the most citations in the last 5 years were Huhn M, Pillinger T, McCutcheon RA, Taipale H and Charlson FJ; and the most cited journals were the American Journal of Psychiatry, JAMA Psychiatry, Schizophrenia Research, Schizophrenia Bulletin and The Journal of Clinical Psychiatry.

The retrieved co-cited reference network (1980–2021) described coherent links between 25 different clusters and permits to expose the evolution of research trends on antipsychotics and schizophrenia, from first generation to second and third generation antipsychotics''.

4.2. Identification of trends and future of evidence synthesis

The obtained co-citation reference network was divided into 25 different clusters; however, we only examined the 23 most relevant clusters. This network proposes a history of research on antipsychotics for schizophrenia from 1980 to 2021 (Fig. 1). Three major trends of research were identified. The most important trend was evolution from first- to 'third-generation antipsychotics' (clusters #14(Carlsson, 1978), #20(McCreadie et al., 1985), #10(Davis et al., 1991), #0(Chouinard et al., 1993), #2(Marder and Meibach, 1994)), which further merged with 'evidence-based psychiatry' in 2011 (cluster #11(Potkin et al., 2003)) and now mainly focused on 'treatment-resistant schizophrenia' (cluster #3(Howes et al., 2017)) and 'real-world effectiveness' (cluster #8(Tiihonen et al., 2011)).

The second major trend concerns cognition in schizophrenia (clusters #25(Goff et al., 1992), #21(Gray et al., 1995), #7(Meltzer and McGurk, 1999), #9(Arnt and Skarsfeldt, 1998), #6(Keefe et al., 2007)); however, this trend of research has decreased since 2007.

The third major research trend concerns treatment side effects starting with metabolic syndrome and its components (#13(Allison et al., 1999); #4(ADA, 2004)) that continue and have now developed in evidence synthesis on metabolic syndrome (cluster #15(Vancampfort et al., 2015)).

A focus on the last five years reveals that the latest trends of research were on treatment-resistant patients, maintenance/discontinuation of antipsychotics, evidence synthesis, and real-world effectiveness. More recently, in 2021, we identified evidence synthesis for negative symptoms, ultra-treatment resistance, the gut microbiome and cannabidiol (Supplementary Figs. 4 and 6).

To complete these findings, the burstness of keywords can help identify the latest trends of research, such as keywords referring to evidence synthesis (guideline, meta-analysis) or most recent trends of research (cannabidiol, discontinuation, nanoparticle) (Supplementary Table 2. AA to DD, Supplementary Fig. 7). These results confirm that evidence synthesis is a predominant trend of the last decade. In addition, most cited articles over the last 5 years were mainly meta-analyses and consensus guidelines (Supplementary Table 2.U.V), and our co-occurring author keywords networks also revealed that the number of network meta-analyses is rapidly increasing.

Although these sixty years of research on antipsychotics and schizophrenia have generated massive data and treatment guidelines, many fundamental gaps in knowledge remain such as: the optimum length of treatment with antipsychotic medication; the heterogeneity in schizophrenia and treatment resistance; or also that current antipsychotic medications are not disease modifying (Howes and Kaar, 2018).

4.3. Relevance of scientometric studies for evidence synthesis

The collaboration network encompasses the network of co-authorship (Fig. 2) of co-authors' countries and institutions (Fig. 1A. B). Combined with the clusters of the co-citation reference network (Fig. 3), researchers can visualize the influence of research teams regarding the generation of scientific knowledge and evaluate possible candidates for research collaborations.

Researchers can benefit from scientometric analyses in several ways (Nakagawa et al., 2019). For instance, the extracted corpus of publication of systematic reviews can be visualized, thereby synthetizing the major trends of research retrieved with selected search terms. Furthermore, the co-occurring author keywords networks and keywords burstness can reveal the most relevant keywords for a specific trend of research and thus help to select a string of keywords for database searches (Janssens and Gwinn, 2015). The evolution of research trends, with the most recent areas of research interest and productivity as well as trends thereof, is identified, with essential intellectual turning point papers that are frequently central papers of clusters (Supplementary Table 1). These turning-point papers are essential to understand the evolution of research trends, and can inform writing of introduction and rationale of systematic reviews (Chen, 2006a).

Specific networks of existing meta-analyses can also be extracted to identify major publications and research groups and help evaluate whether additional meta-analyses are required on a specific topic or if bursts of literature appear in a certain area, indicating the need for new meta-analysis (Ioannidis, 2016). Several limitations could also be more easily considered, such as publication years, methodological differences, or citation bias.

Finally, journal analysis and co-cited journal analysis can provide important information that can help researchers select the most appropriate journals for article submission (Supplementary Fig. 10).

4.4. Strengths and limitations

To the best of our knowledge, this is the first scientometric study on antipsychotics in schizophrenia.

Compared to narrative reviews, scientometric analyses can comprehensively guide clinicians and scholars on the history of research and emerging trends. Also, they can provide a synopsis of clinically relevant questions that have been poorly addressed in research, potentially informing future trials, although evidence synthesis methods are still not adequately taken into account in the design of future trials (Nikolakopoulou et al., 2019). Moreover, this work can help identify the most important authors and journals in the field of antipsychotics in schizophrenia, can guide more junior investigators in identifying mentors and institutions to seek out and inform stakeholders, policy-makers, and funding agencies on the directions of the clinical and scientific community using and studying antipsychotics (O'Leary et al., 2017).

The fact that the authors of this work have already published several

systematic reviews on this topic and analyzed retrieved nodes when implementing networks in CiteSpace to detect possible errors, such as homonyms of the author, further helps to strengthen the quality of analysis. Considering the important number of references included and the good reliability of consistent clusters, we consider that the overall quality of our analysis is solid; however, we cannot exclude that some aberrant clusters were obtained.

An important limitation of scientometric studies is the use of citation-related indicators, as scientometric studies can be a source of different biases, in particular, citation bias. Regardless of its quality or relevance, a reference can be cited for the sole purpose of underscoring the quality of a manuscript, thereby contributing to the underutilization of available evidence. Different parameters can contribute to citation bias, including self-citations, the authority of the author, journal impact factor, and the journal where the manuscript was accepted (Urlings et al., 2021). Additional potential biases include bias against novelty, outcome reporting bias, location bias, and publication bias (Wang et al., 2017).

Publication bias consists of favoring publication of studies with significant results, withholding negative results from publication (Jannot et al., 2013; Joober et al., 2012). To address such limitations when comprehensively synthesizing the collaborative network and measuring scientific impact, novel measures of research combining bibliometric indicators, peer review results and altmetrics with more accurate assessments of scientific research are needed (Fenner, 2014).

One important bias that can be detected by a detailed examination of hotspots in the retrieved networks is citation distortion, consisting of distortions in the persuasive use of citations that can be used to establish unfounded scientific claims as fact (Greenberg, 2009).

Another limitation is that the gathered data were only obtained from WOSCC, which can lead to a relative incompleteness of the retrieved publication (Singh et al., 2021; Visser et al., 2021). For most databases, such as PubMed, Embase, and the Cochrane Database of Systematic Reviews, full text and citation analyses are not available. Nevertheless, WOSCC is considered the most suitable database of scientometric studies, and the future development of software could make it possible to simultaneously analyze results from different databases with reliable automatic duplicate removal.

Of importance, our co-citation network only focused on first authors, which does not adequately reflect the authors' influence. In addition, some keywords have different expressions, which can affect clustering even after our checking procedure. Finally, more recent trends are not necessarily detected by the various co-cited networks since most recent publications are not sufficiently cited.

5. Conclusion

This scientometric study provides historical insight and perspectives on research and publications on antipsychotics in schizophrenia research. The number of published papers significantly increased over the last 30 years, reaching a peak in 2010, followed by an average of more than 1400 articles per year. Most influential countries, institutions, and authors were identified, as were hotspots and the latest trends of research, such as resistant-treatment schizophrenia, maintenance/discontinuation of antipsychotics, evidence synthesis, real-world effectiveness and new antipsychotic formulations. More collaboration is needed between institutions from the United States of America, European institutions, and the emerging influence of China. Our study provides useful information for researchers to understand the evolution of research on antipsychotics in schizophrenia and promises to provide useful information for researchers, grant applicants, funding agencies, and policy-makers.

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Conflict of interest

Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Relmada, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Rovi, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of LB Pharma.

Heidi Taipale reports personal fees from Janssen-Cilag and Otsuka.

Jari Tiihonen reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka. He is a member of the advisory board for Lundbeck and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation. He has been a consultant and/or advisor to and/or has received honoraria from Eli Lilly, Evidera, Janssen-Cilag, Lundbeck, Orion, Otsuka, Mediuutiset, Sidera, and Sunovion.

Jari Tiihonen, Antti Tanskanen and Heidi Taipale have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution.

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

Stefan Leucht received honoraria as a consultant/advisor and/or for lectures from Angelini, Böhringer Ingelheim, Geodon&Richter, Janssen, Johnson & Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofiAventis, Sandoz, Sunovion, TEVA, Eisai, Rovi, Medichem.

Stefan Kaiser received royalties for cognitive tests and training software from Schuhfried.

Toby Pillinger has participated in educational speaker meetings organized by Lundbeck, Otsuka, Sunovion, Schwabe Pharma and Recordati.

Chaomei Chen and Michel Sabe report no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104608.

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