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ORIGINAL RESEARCH

Bibliometric Analysis on GABA-A Receptors Research Based on CiteSpace and VOSviewer

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Background: GABA-A receptors are the primary mediators of brain inhibitory neurotransmission. In the past years, many studies focused on this channel to decipher the pathogenesis of related diseases but lacked bibliometric analysis research. This study aims to explore the research status and identify the research trends of GABA-A receptor channels.

Methods: Publications related to GABA-A receptor channels were retrieved from the Web of Science Core Collection from 2012 to 2022. After screening, the VOSviewer 1.6.18 and Citespace 5.8 R3 were used for bibliometric analysis from journals, countries, institutions, authors, co-cited references and keywords.

Results: We included 12,124 publications in the field of GABA-A receptor channels for analysis. The data shows that although there was a slight decrease in annual publications from 2012 to 2021, it remained at a relatively high level. Most publications were in the domain of neuroscience. Additionally, the United States was the most prolific country, followed by China. Univ Toronto was the most productive institution, and James M Cook led essential findings in this field. Furthermore, brain activation, GABAAR subunits expression, modulation mechanism in pain and anxiety behaviors and GABA and dopamine were paid attention to by researchers. And top research frontiers were molecular docking, autoimmune encephalitic series, obesity, sex difference, diagnosis and management, EEG and KCC2.

Conclusion: Taken together, academic attention on GABA-A receptor channels was never neglected since 2012. Our analysis identified key information, such as core countries, institutions and authors in this field. Molecular docking, autoimmune encephalitic series, obesity, sex difference, diagnosis and management, EEG and KCC2 will be the future research direction.

Keywords: GABA-A receptor, GABA, visual analysis, trends, CiteSpace, VOSviewer

Introduction

Gamma-aminobutyric acid (GABA) is a key mediator of brain activity in mammals, acting as an inhibitory neurotransmitter.[1–3] There is a critical role for GABAergic neurotransmission in neurodevelopmental disorders.[4] Two types of receptors mediate GABA's inhibitory effects, GABA-A receptors and GABA-B receptors.[5,6] As ligand-gated ion channels, GABA-A receptors are heteropentamers formed from a selection of 19 subunits and one of the most significant drug targets[7] in the treatment of neuropsychiatric disorders, such as depression,[8] aggression, anxiety,[9] and insomnia.[10] Genetic studies have documented the relationship between GABA-A receptor subunit genes and epilepsy,[11] eating disorder,[12] autism,[13] and bipolar disorders.[14] Besides, there is also interest in GABA-A receptors as potential targets for Parkinson disease and other neurological dysfunctions,[15] essential tremor,[16] ischemic stroke,[17] pain management.[18] Even some of the World's major insecticides.[19–21]

As research in the GABAARs continues to expand, the literature also continues to progress. Despite this, the topics and characteristics of publications on the GABA-A receptor channels have not been investigated. Bibliometric analysis has been widely used to explore research hotspots and frontiers in specific fields based on the productivity of countries,

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institutions, authors, and keywords.[22,23] Using bibliometric analysis and visual analysis, we analyzed scientific publications on GABA-A receptor channels from 1999 to 2022, and we hope to provide researchers with insight into their hotspots and emerging directions.

Data Source and Search Strategy

On July 30, 2022, a data search was conducted. The data for analysis were retrieved from the Science Citation Index Expanded (SCI-expanded) of the Web of Science Core Collection (WoSCC) database from 2012 to 2022. Different from databases like Scopus, Derwent, China national knowledge infrastructure (CNKI), and the Chinese social sciences citation index (CSSCI), WoSCC includes more scientific publications and is usually regarded as the data source for bibliometric software. The search keywords entered into the database were as follows: TS =(GABA-A Receptor OR GABA A Receptor OR gamma-Aminobutyric Acid Subtype A Receptors) and language: (English).

Data Collection

Bibliographic information of every included publication was collected by downloading, screening, sorting, and extracting from WoSCC independently by two authors, including publication year, author, journal, country, institution, co-cited references and keywords. The retrieval strategy of the experiments is shown in Figure 1.

Statistical Analysis

We counted the number of publications every year.[24] The VOSviewer 1.6.18[25] was used to identify top countries, institutions, authors, and journals. The Citespace 5.8 R3[26] analysed co-cited references and keywords for trends. Maps that visualize knowledge contain nodes and links. Each node in a map represents an institution, country, author, or keyword. Purple circles indicate nodes with high centrality, usually considered turning points or pivotal points in a field.

Results

General Information and Annual Publication Output

12,124 articles related to GABA-A receptor channels were retrieved. Based on the search results for GABA-A receptor channels in WOS, publication growth on this topic can be divided into 2 stages, a slow growth phase from 2012 to 2014 and a slow decrease phase from 2015 to 2022 (Figure 2). In the past ten years, the output peaked in 2014 (1263 articles). In general, the research in this field is relatively stable and has maintained a high output in the past decade, indicating the importance of this field.

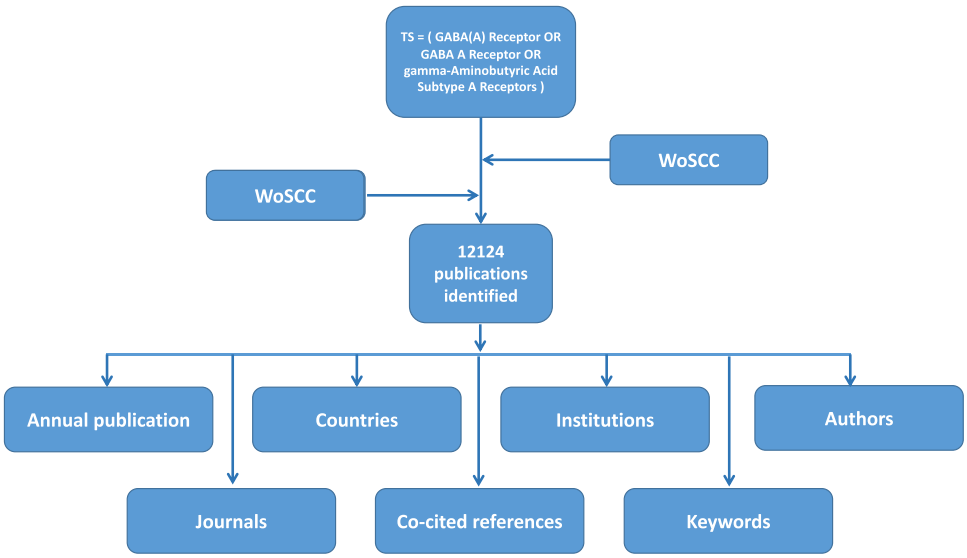

Figure 1 Flow chart for the analysis of GABA-A receptor channels research.

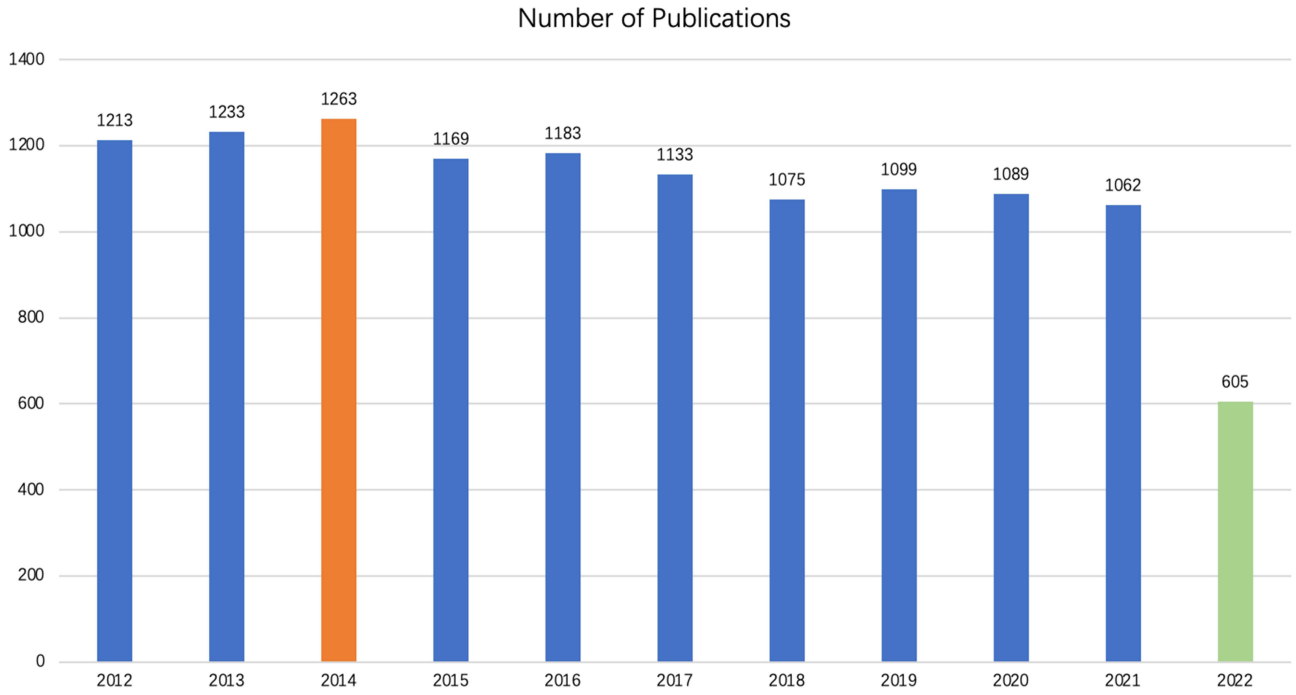

Figure 2 Publication outputs of GABA-A receptor channels research.

Active Journals

By analyzing journals, we can identify the core journals in this field. Table 1 presents the top 10 journals by the number of publications in the field. Journal of Neuroscience (455 publications) ranks first, followed by Neuropharmacology (354 publications) and PLoS One (335 publications). Among the top 10 journals, there are 3 journals with impact factors >5, including the Journal of Neuroscience (6.709), Frontiers in Cellular Neuroscience (6.147), and Psychopharmacology (5.273). Furthermore, of the top 10 journals, 5 are from the US, 3 from England, and 2 from the Netherlands.

Active Countries and Institutions

Scientific collaborations can be determined in this field by institutional cooperation networks and national cooperation networks using Citespace.[27] Figure 3 displays the largest cooperation network of the 112 productive countries/regions. The size of the circles represents the number of publications of countries/regions, and the shorter distance between the two circles suggests more collaboration between individual countries/regions. The purple rings outside the circle refer to centrality. As we can see, the USA

Table 1 Top 10 Journals That Published Publications on GABA-A Receptor Channels

Ranking	Journal	Frequency	JCR	IF	Country
1	Journal of Neuroscience	455	Q1	6.709	USA
2	Neuropharmacology	354	Q1	5.273	England
3	PLoS One	335	Q2	3.752	USA
4	Neuroscience	326	Q3	3.708	England
5	Scientific Reports	204	Q1	4.996	England
6	Journal of Neurophysiology	199	Q3	2.974	USA
7	Behavioural Brain Research	172	Q2	3.352	Netherlands
8	Frontiers in Cellular Neuroscience	172	Q1	6.147	Switzerland
9	Neuroscience Letters	157	Q3	3.197	Netherlands
10	Psychopharmacology	155	Q2	4.415	Germany

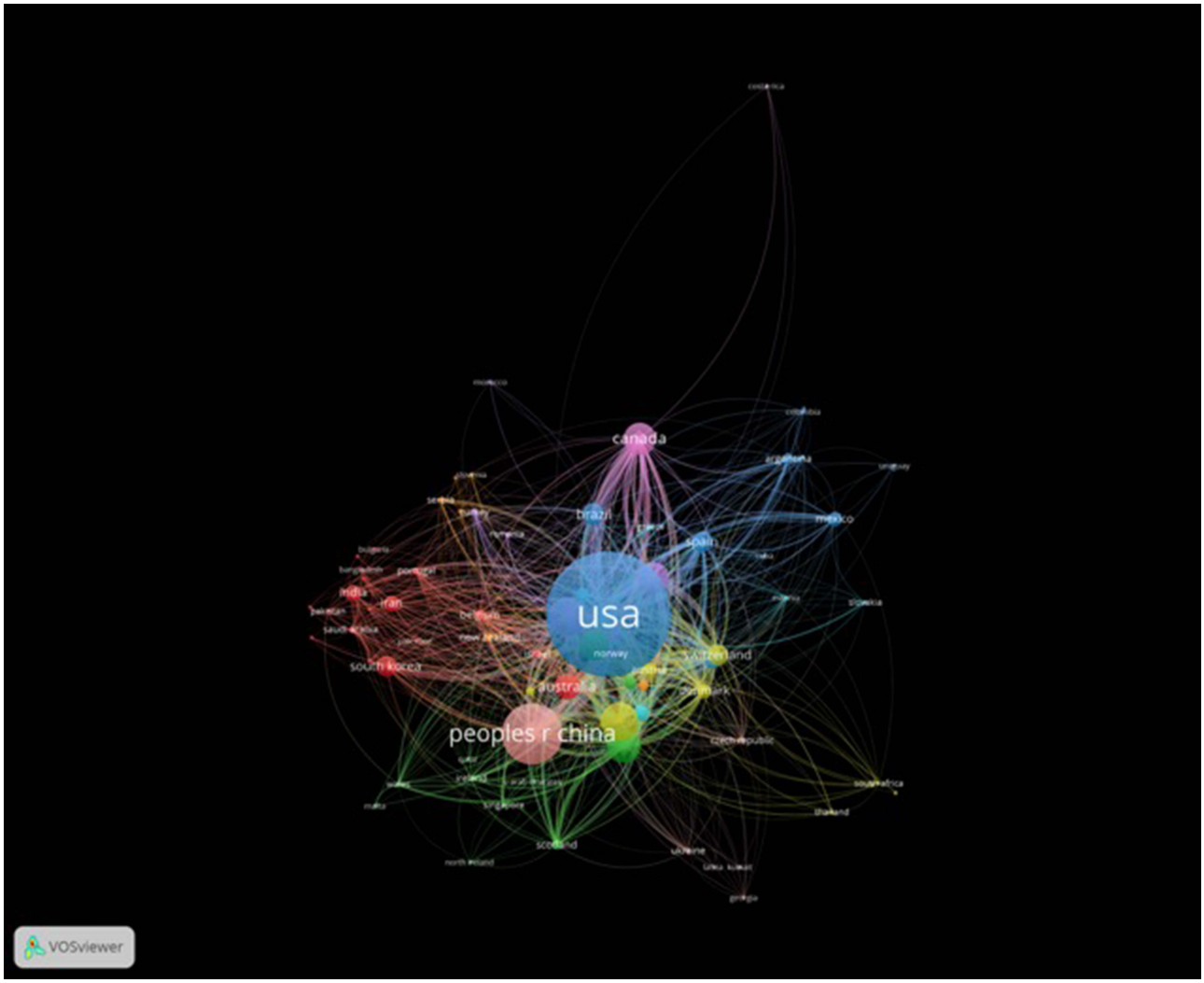

Figure 3 Cooperation network of the top 112 productive countries/regions.

(4658 publications) ranks first in the publication quantity, which is followed by PEOPLES R CHINA (1679 publications) and GERMANY (872 publications). Furthermore, Table 2 shows the top 5 institutions and countries/regions that contributed to the GABA (A) Receptor channel research publications. Of them, Univ Toronto (175 publications) was the most productive country, followed by Harvard Univ (160 publications), UCL (156 publications), Univ Pittsburgh (150 publications) and Univ Wisconsin (150 publications). A network map of 1157 of 7216 institutions researching GABA (A) Receptor channels with frequency over five is shown in Figure 4.

Table 2 Top Five Institutions and Countries Contributed to GABA-A Receptor Channels

Ranking	Country/Region	Frequency
1	USA	4658
2	Peoples R China	1679
3	Germany	872
4	Japan	868
5	England	707

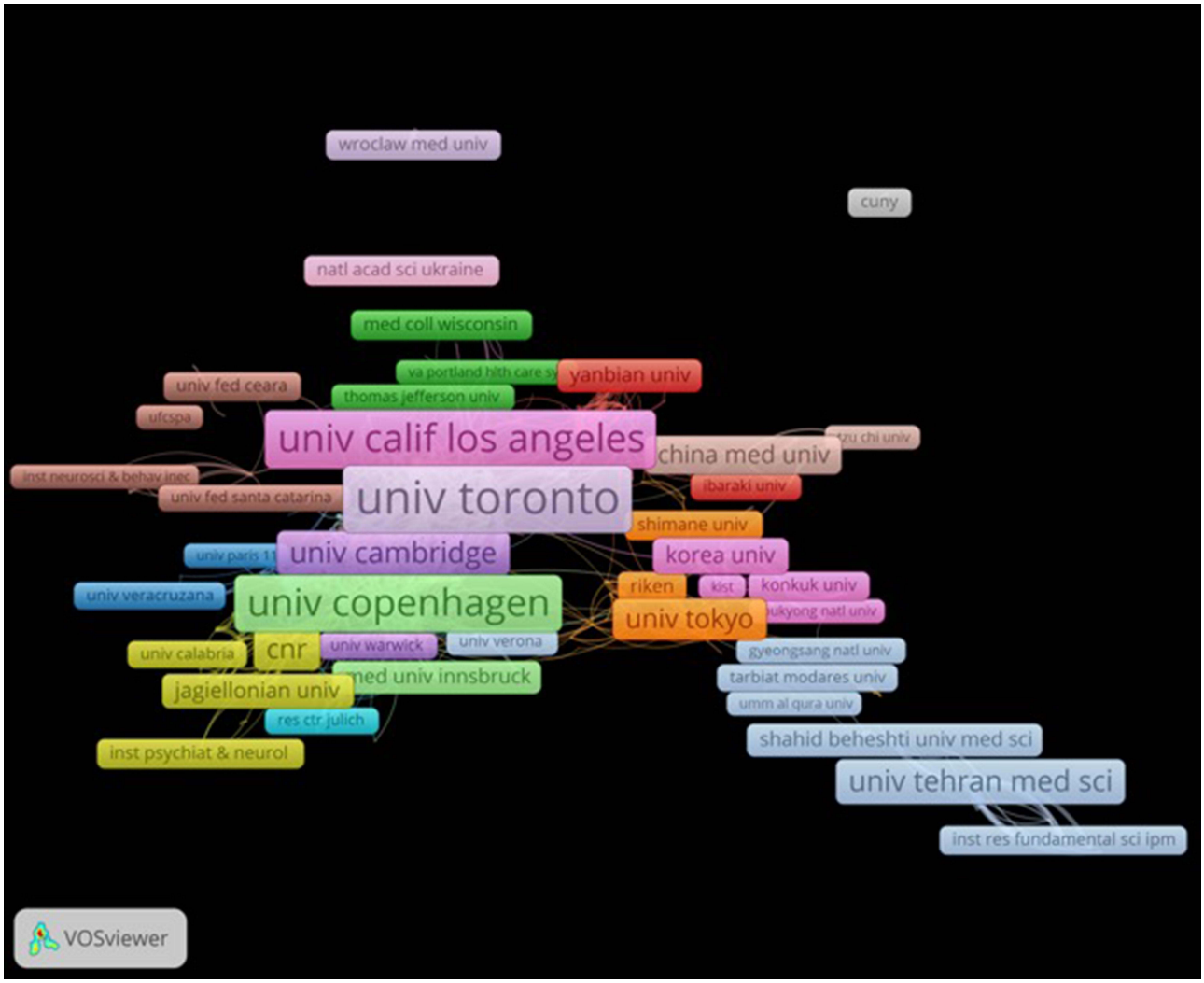

Figure 4 Network map of 1157 of 7216 institutions with a frequency of more than five researching GABA-A receptor channels.

Active Authors

Analysis of active authors could help us identify the core authors in this field. A total of 45,353 authors contributed 12,124 articles in this field. The network of contributing authors is demonstrated in Figure 5. Table 3 lists the top five most active authors. As we can see, James M Cook (94 publications), Bettler Bernhard (43 publications), Ernst Margot (43 publications), Chebib Mary (42 publications), and Rudolph Uwe (42 publications) are the top five active authors in this field. Although many authors have published relevant articles, there was little collaboration among them, suggesting that more high-quality and large-scale collaborations are needed.

Co-Cited References

To determine the key knowledge base in the field, the top five cited references about frequency are shown in Table 4, Figure 6. As we can see, the first ranked citation in terms of frequency was the article in NATURE titled "Crystal structure of a human GABAA receptor".[28] In this experimental work, Miller PS provided a detailed structure of a human GABAA receptor. Besides, the publication with the most incredible burst intensity (48.4) is "GABAA receptor signaling mechanisms revealed by structural pharmacology"[29] by Masiulis S, which reveals multiple aspects of receptor activation and provides a path for the rational design of subunit-specific GABA-A receptor modulators. In addition, most of them are reviews bringing us research progress in this field.

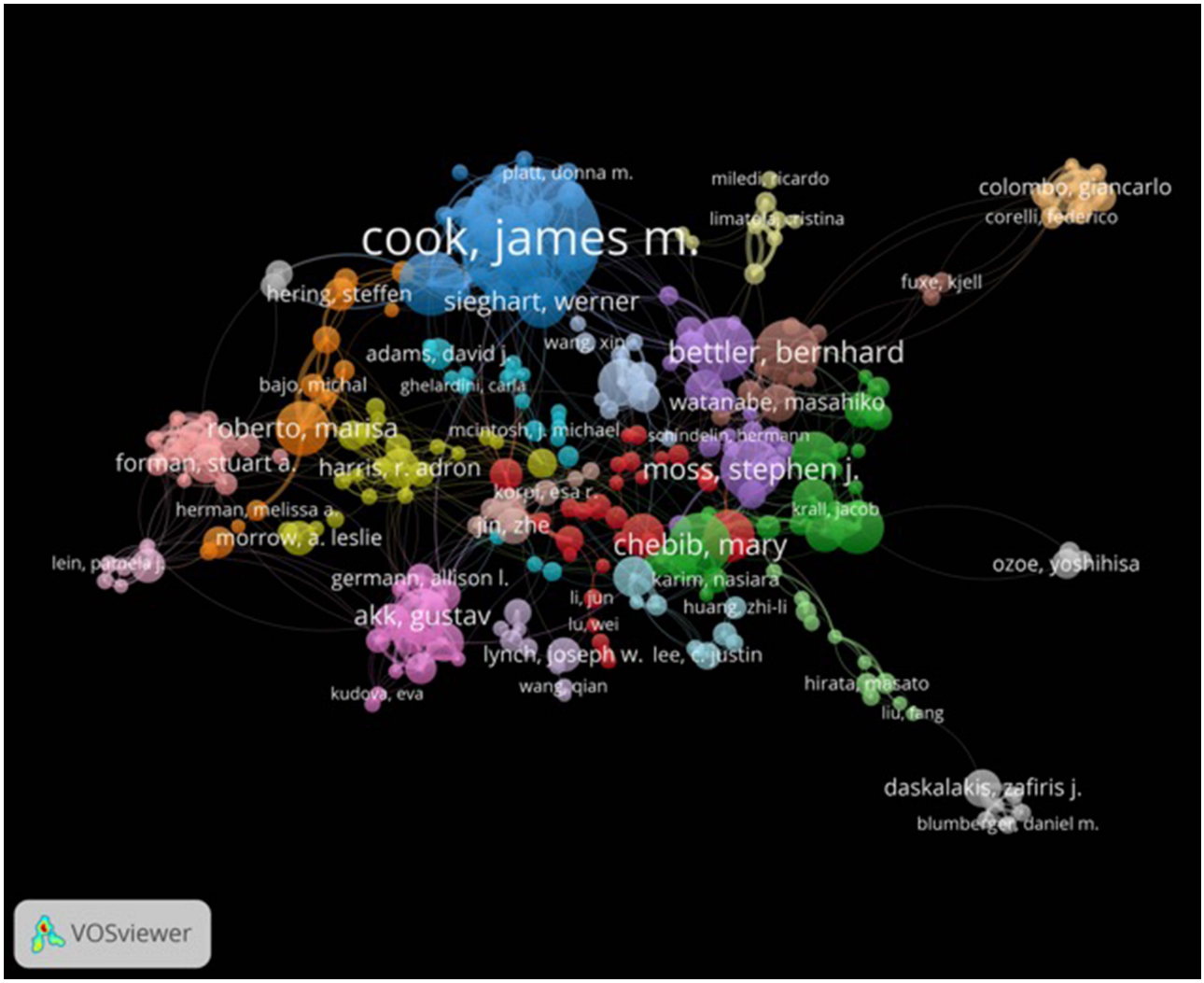

Figure 5 Network map of authors who conducted GABA-A receptor channels with publications over ten.

Keyword Co-Occurrence and Burst

Research hot topics can be described by keyword co-occurrence analysis, and burst keywords can reflect research frontiers over time.[30] CiteSpace was used to construct an acknowledge map of keyword co-occurrence (Figure 7) and identified the top 10 keywords from 1912 to 2022 (Table 5) according to frequency and centrality. The top keywords were "expression" and "neuron", with a frequency of more than 1000 times. And "dopamine neuron", "projection", "central amygdala", and "chronic pain" are core keywords with a centrality of more than 0.18.

Table 3 Top Five Authors That Published Articles on GABA-A Receptor Channels

Ranking	Author	Documents	Citations
1	Cook, James M	94	1168
2	Bettler, Bernhard	43	1286
3	Ernst, Margot	43	755
4	Chebib, Mary	42	747
5	Rudolph, Uwe	42	936

Table 4 Top 10 Co-Cited References in Terms of Frequency on GABA-A Receptor Channels

Ranking	Freq	Burst	Centrality	Author	Year	Title	Source
1	160	40.8	0.04	Miller PS	2014	Crystal structure of a human GABAA receptor	NATURE
2	157	20.01	0.08	Brickley SG	2012	Extrasynaptic GABAA Receptors: Their Function in the CNS and Implications for Disease	NEURON
3	153	17.84	0.04	Hibbs RE	2011	Principles of activation and permeation in an anion-selective Cys-loop receptor	NATURE
4	111	48.4	0.03	Masiulis S	2019	GABAA receptor signalling mechanisms revealed by structural pharmacology	NATURE
5	110	17.53	0.07	Rudolph U	2011	Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes	NAT REV DRUG DISCOV
6	106	13.23	0.04	Luscher B	2011	GABAA Receptor Trafficking-Mediated Plasticity of Inhibitory Synapses	NEURON
7	105	34.26	0	Olsen RW	2009	GABAA receptors: Subtypes provide diversity of function and pharmacology	NEUROPHARMACOLOGY
8	100	40.06	0.04	Zhu ST	2018	Structure of a human synaptic GABAA receptor	NATURE
9	97	25.34	0.09	Rudolph U	2014	GABAA Receptor Subtypes: Therapeutic Potential in Down Syndrome, Affective Disorders, Schizophrenia, and Autism	ANNU REV PHARMACOL
10	91	18.91	0.03	Sigel E	2012	Structure, Function, and Modulation of GABAA Receptors	J BIOL CHEM

On the other hand, strong citation bursts were used to identify and analyze research hot topics, frontiers, and emerging trends over time (Figure 8). As shown in Figure 8, the red line indicates the period during which the burst keyword appears.[31] The citation burst time of keywords including molecular docking, autoimmune encephalitic series, antibody, obesity, reveal, EEG, diagnosis, sex difference, kcc2, molecular dynamics, and management.

Discussion

The explosive growth of research literature has brought difficulties in grasping scientific research progress. But bibliometric analysis is a widely accepted method that has emerged in recent years, providing experienced researchers with systematic and visual knowledge structures and helping new scientific researchers to get the general trends in their field.[30,32,33]

Here, we conduct a bibliometric analysis of research on GABAAR channels to gain insight into its current research status and characteristics.12,124 articles on "GABA-A Receptor channels" were published in the past ten years. The current analysis of annual publication output reflects that the research heat of GABAAR channels tends to be stable, and scientific research is progressing steadily. Notably, the outputs reached a peak in 2012 and "Extra-synaptic GABAA Receptors: Their Function in the CNS and Implications for Disease"[34] was published in Neuron in 2012, suggesting its therapeutic target for the treatment of these diseases. Besides focusing on contributing journals, we could find that the Journal of Neuroscience is the leading journal in GABAAR research. Journal of Neuroscience publishes papers on a broad range of topics of general interest to those working on the nervous system, reflecting the close relationship between GABAAR and neuroscience.

From the perspective of scientific research cooperation, there is closer cooperation among countries, institutions and authors. Among the 112 countries and regions, the USA (4658 articles) is the leading country, followed by PEOPLES R CHINA (1679 articles). However, there is still a significant gap in research output between China and the United States, which is twice that of China. Besides, Univ Toronto is the most productive university and the core institution of GABAAR research, attracting researchers in related fields. However, the most prolific author James M Cook is from

Figure 6 Analysis of co-cited references on GABA-A receptor channels.

University of Wisconsin-Milwaukee. Therefore, the latest research trends can be followed by the above-mentioned high-yield national institutions and authors.

Highly cited references are classic studies that mainly address the structure and mechanisms of GABAA receptors focusing on the pharmacology revealed. For example, Miller PS's publication[28] and Brickley SG's study.[34] Table 4 lists the top 10 co-cited references regarding frequency on GABA A Receptor channel. As we can see, most articles are published in journals with high-impact factors, such as Nature, which shows the importance of research in this field. For instance, Miller PS's paper titled "Crystal structure of a human GABAA receptor" presents the first three-dimensional structure of a GABAAR, revealing architectural elements unique to eukaryotic Cys-loop receptors, explains the mechanistic consequences of multiple human disease mutations and showing an unexpected structural role for a conserved N-linked glycan. Brickley SG's paper titled "Extrasynaptic GABAA Receptors: Their Function in the CNS and Implications for Disease"[34] suggested that extrasynaptic GABA(A) Rs could be regarded as therapeutic targets

Table 5 Top 10 Keywords in Terms of Frequency and Centrality on GABA-A Receptor Channels

Ranking	Freq	Keyword	Ranking	Centrality	Keyword
1	1231	Expression	1	0.24	Dopamine neuron
2	1097	Neuron	2	0.2	Projection
3	992	Activation	3	0.18	Central amygdala
4	947	Brain	4	0.18	Chronic pain
5	927	Rat	5	0.17	Neuropathic pain
6	826	Modulation	6	0.17	Anxiety like behavior
7	815	Inhibition	7	0.17	Subunit composition
8	787	Mechanism	8	0.17	Extinction
9	717	Gaba	9	0.16	Stimulation
10	505	Subunit	10	0.16	Association

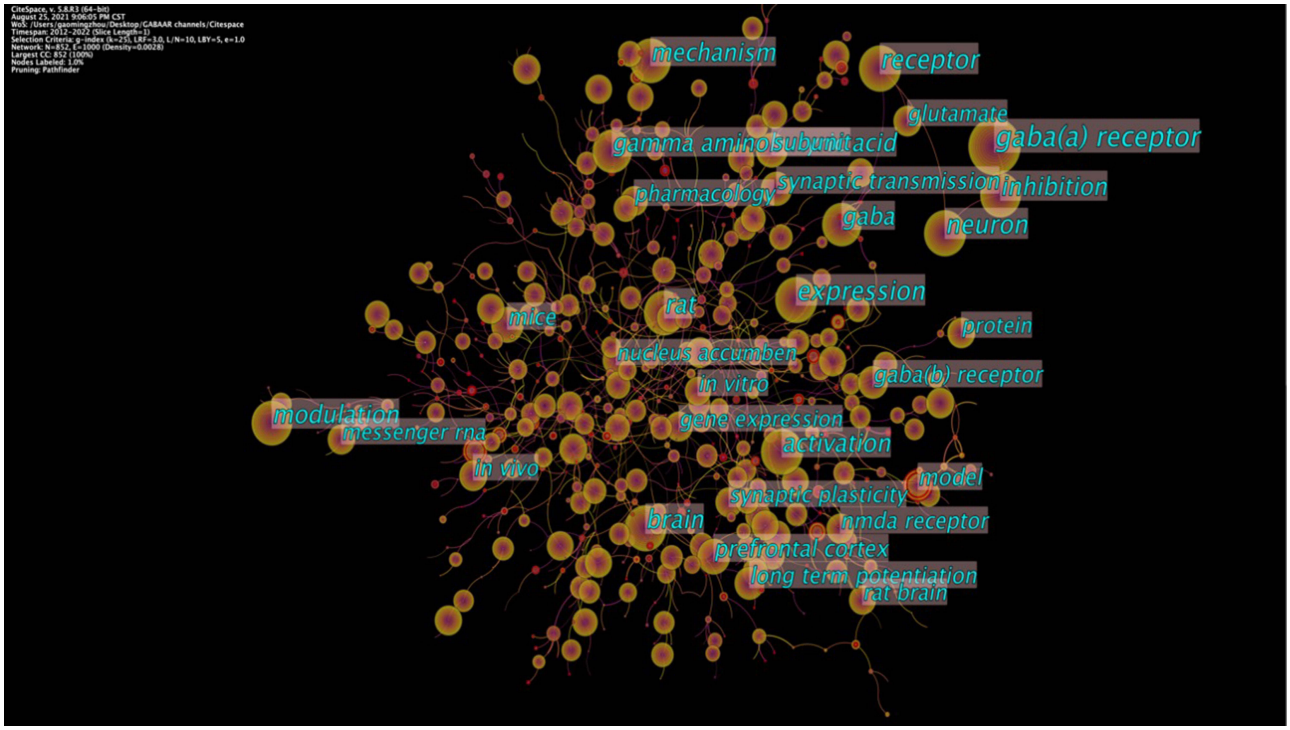

Figure 7 Analysis of keywords on GABA-A receptor channels.

for the treatment of CNS diseases. Hibbs RE's paper titled "Principles of activation and permeation in an anion-selective Cys-loop receptor"[35] presents the first three-dimensional structure of an inhibitory anion-selective Cys-loop receptor. Masiulis S's paper titled "GABAA receptor signalling mechanisms revealed by structural pharmacology"[29] provides a structural framework to integrate previous physiology and pharmacology research and a rational basis for developing GABAA receptor modulators. Rudolph U's paper titled "Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes"[36] suggested that receptor subtype-selective compounds could overcome the limitations of classical benzodiazepines; furthermore, they might be valuable for novel indications, such as chronic pain, depression, schizophrenia, cognitive enhancement, and stroke.

Furthermore, keyword co-occurrence indicates current hotspots, such as brain activation, GABAAR subunits expression, modulation mechanism in pain and anxiety behaviour, and GABA and dopamine.

Brain Activation

In neuroscience, brain activation has always been a research hot topics. Abnormal activation of the central amygdala is a vital direction.[37–39] Furthermore, abnormal brain activation in patients with diseases where GABAAR plays an important role has been found, like premenstrual dysphoric disorder.[40] A deeper activation mechanism could be located at GABAAR. And distribution, density, and activity of receptors in the brain can be visualized by brain imaging technology.[41] Research shows that Radixin regulates synaptic GABAA receptor density to reverse learning and short-term memory.[42] And activation of GABAA receptors enhances behavioral recovery in the brain.[31]

Expression and Function of GABAAR Subunits

The GABAARs are constituted from different subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3), involving different functions referring to abnormal expression of GABAA receptor subunits.[43] For instance, the zebrafish model of gabra1 deficiency proved that GABRA1 might regulate brain development.[44] β3 subunit is a critical player in GABAAR performance and an essential contributor to the appearance of severe neurological disorders, such as epilepsy, autism, and other syndromes.[43] And an aberrant expression of GABAAR subunits α1 and β2 in the stargazers is unlikely to

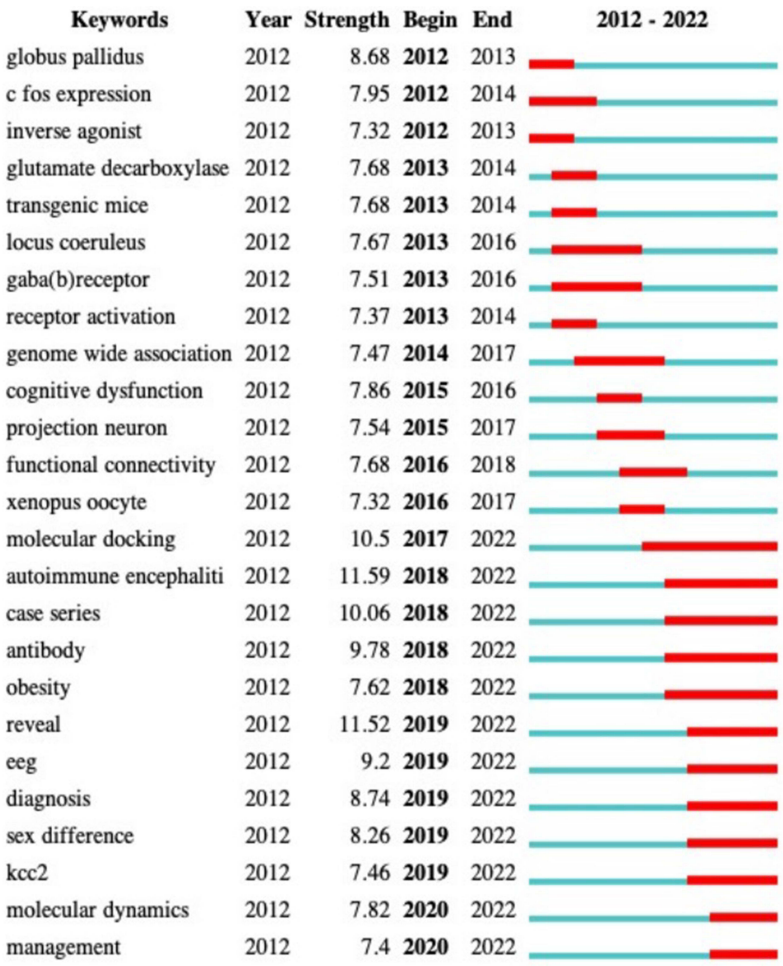

Figure 8 Top 25 keywords with the most robust citation bursts on GABA-A receptor channels.

directly contribute to the initiation of absence seizures.[45,46] δ-GABAARs mediate a slow constant inhibitory current called tonic inhibition during health and disease.[47] Therefore, at the current stage, the regulatory functions of GABAAR subunits under different expressions are becoming more and more significant in life activities and diseases.

Modulation Mechanism in Pain and Anxiety Behavior

As positive and negative allosteric modulators, GABAA receptors are abundant in the central nervous system and are prolific drug targets for treating anxiety.[48] GABAA-receptor dysfunction in patients as a causal predisposition to anxiety disorders. F Crestani's finding proved that GABAA-receptor dysfunction in patients is a causal predisposition to anxiety disorders.[49] Notably, GABAA(δ)R plays a vital role in regulating anxiety-like behavior proved by rats.[50] Giorgia Quadrato's study shows that the NFATc4-dependent increase in hippocampal neurogenesis after GABAAR stimulation is required to suppress the anxiety response in mice.[51,52] Besides, GABAkines discovery are also ongoing to identify novel drug for the treatment of acute and chronic pain.[53]

Keyword burst indicating future research direction, such as molecular docking, autoimmune encephalitic series, obesity, sex difference, EEG and KCC2.

Molecular Docking

Molecular docking technology is a new technology based on computer technology that assists drug molecular design.[54] This technology starts from the receptors and ligands with known structures to identify the interactions between molecules and predict the best binding mode between two molecules. For now, it is used to explore the potential targets and action mechanisms of

effective components of traditional Chinese medicine.[55] Abnormal GABA receptor pathway is common in psychiatric diseases, such as abnormal GABAergic system in the brain of schizophrenics.[56] GABA exerts biological activity through GABA receptors (mainly GABAAR). However, previous studies have not found evidence of a direct combination of antipsychotic drugs and GABAAR, and the mechanism of antipsychotic drugs regulating GABAAR is still unclear. But there is also evidence that selective alpha1-GABA-A positive allosteric modulators exert antipsychotic activity.[57] Drug research on anti-anxiety targets of GABAAR is also a research hotspot.[58] Molecular docking technology is an important early foundation and also a research hotspot in the future.

Autoimmune Encephalitic Series

Autoimmune encephalitis (AE) belongs to neuron-related antibody encephalitis. The main neuropathological characteristics of AE are the infiltration of lymphocytic inflammatory cells into brain parenchyma and the formation of sleeve-like structures around blood vessels, one of the focuses of many neuroimmunological studies.[59] From the pathogenesis perspective, AE is a disease caused by the antigen–antibody reaction on the cell surface or in the cell of the central nervous system, γ Aminobutyric acid receptor (GABAR, GABAR is divided into GABA-A R and GABA-B R) is one of them.[60] Research shows that epileptic seizures are the most common in anti-LGI encephalitis and anti-GABAR encephalitis. Still, the latter has an acute onset, both autoimmune synaptic encephalitis. LGI1 acts with epilepsy-related proteins ADAM22 and ADAM23.[61] Anti-GABAR can change synaptic function, but patients with anti-GABAR encephalitis have early, frequent seizures or status epilepticus.[62] More in-depth research on pathogenesis and treatment is still in progress.

Obesity

Obesity can lead to a higher risk of early death and increase overall mortality. It has become a global "epidemic" associated with various chronic diseases. The research shows that the GABAergic signal in the nucleus accumbens can regulate the expression of MCH in neurons of the lateral hypothalamus. The sensitivity of MCH neurons in LHA of obese rats to satiety signal decreases, and reward feeding increases.[63] In addition, energy metabolism and obesity-related diseases are severe threats to human health. In addition to the direct involvement of the central nervous system in regulating the peripheral digestive system, the central nervous system can further influence feeding behaviour through the feeding "reward" pathway, thus regulating energy metabolism. Nucleus accumbens (NAc) contain GD neurons that receive afferent information from gastric mechanical traction stimulation, and the altered excitation of these neurons may be associated with changes in gastric motility. GABA-A receptor activation is an important factor in this regulation, and the Glucagon-like peptide 1 (GLP-1) receptor signaling pathway is also involved in regulating this process.[64] Recent studies indicated that high comorbidity between obesity and mental disorders often exacerbates metabolic and neurological symptoms significantly. Reciprocal control of obesity via a GABAAR is becoming more and more important.[65]

Sex Difference

Gender differences exist in many life activities and disease processes.[66] Gender differences in depression first appear in adolescence, women are more likely to be depressed, and this trend will continue into adulthood; the incidence of men and women is about 1:2.[67] The study confirmed that THIP exerts rapid antidepressant effects on prepubertal and early adolescent female mice models of depression caused by chronic stress through activation of the δ-GABAAR subunit, providing a new idea for the treatment of clinical depression in teenage females.[68] Future studies focusing on gender differences in the pathogenesis of GABAAR are potential research directions.

EEG and KCC2

Electroencephalography (EEG) is the acquisition of microvolt-level electrical signals generated by synchronised neuronal activity within the brain by electrodes placed at specific locations on the scalp. The GABAAR pathway has significant research potential for excitability in the human brain.[69] In addition, the excitatory effects of GABA mainly depend on the intracellular chloride concentration of neurons, in which Na^+-K^+-Cl^- cotransporter 1 (NKCC1) promotes intracellular Cl^- accumulation, while K^+-Cl^- cotransporter 2 (KCC2) excludes intracellular Cl^- and decreases intracellular Cl^- concentration. Therefore, the association of KCC2 with GABAAR channels has also been investigated.[70]

Limitation

To the best of our knowledge, this is the first study to illustrate trends in GABAAR research over the past decade using bibliometric analysis. We present the first comprehensive research posture of the GABAAR pathway, facilitating researchers to target their research directions and conduct more in-depth studies. Due to the limitation of Citespace software, we use WoSCC as the source of publications, and may ignore publications of other databases, such as patents. However, the WoSCC database is widely recognized in the field of bibliometrics, and its results are reliable.

Conclusions

Based on the WoSCC database, we comprehensively analysed the research status and trends of the GABAAR channels by mapping the knowledge map of authors, institutions, keywords, and so on. The United States was the most prolific country. And Univ Toronto was the most productive institution, and James M Cook led essential findings. Furthermore, the structure and signalling mechanisms of the GABAA receptor are the current knowledge structure. Research hot topics were brain activation, GABAAR subunits expression, modulation mechanism in pain and anxiety behaviors, and GABA and dopamine. And top research frontiers were molecular docking, autoimmune encephalitic series, obesity, sex difference, diagnosis and management, EEG and KCC2.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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