Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Knowledge Atlas of the Co-Occurrence of Epilepsy and Autism: A Bibliometric Analysis and Visualization Using VOSviewer and CiteSpace

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Objective: This study aimed to analyze research on epilepsy in autism and autism in epilepsy using VOSviewer and CiteSpace to identify research hotspots and future directions.

Methods: We searched the Web of Science Core Collection (WoSCC) for relevant studies about epilepsy in autism and autism in epilepsy published from inception to 31 May 2022. VOSviewer and CiteSpace were used to analyze the authors, institutions, countries, publishing journals, reference co-citation patterns, keyword co-occurrence, keyword clustering, keywords with citation bursts, and other aspects to construct a knowledge atlas.

Results: A total of 473 publications related to epilepsy/autism were retrieved. The number of publications about epilepsy/ASD has generally increased over time, with some fluctuations. The USA (202 papers) and University of California-Los Angeles (15 papers) were the leading country and institution, respectively, in this field. Frye, Richard E. was the most published author (9 papers). Notably, collaboration between institutions, countries, and authors does not appear to be active. Hot topics and research frontiers include intellectual disability and exploring the mechanism of epilepsy/ASD from a genetics perspective.

Conclusion: This analysis identified the most influential publications, authors, journals, institutions, and countries in the field of epilepsy/ASD research. Using co-occurrence and evolution analyses, the status of the field was identified and future trends were predicted.

Keywords: epilepsy, autism, bibliometrics, VOSviewer, CiteSpace, visualization analysis

Introduction

Epilepsy is a chronic neurological disorder with diverse etiologies, while autism spectrum disorder (ASD) is a collection of neurodevelopmental disorders with multiple etiologies. The prevalence of these conditions in the general population is 0.6% and 1%, respectively.[1,2] Both conditions seriously affect patients' health and life and pose a huge burden on society.[3,4] Notably, epilepsy and autism often co-occur. In recent years, numerous studies have discussed the relationship between epilepsy and autism and the prevalence of their co-occurrence.[5–10] Amiet et al emphasized that epilepsy in autism is associated with intellectual disability (ID) and reported that the prevalence of epilepsy/ASD with ID (21.5%) was higher than epilepsy/ASD without ID (8%).[10] The US National Survey of Children's Health reported that the prevalence of epilepsy with ASD in 2011–2012 was 8.6%.[8] Lukmanji et al demonstrated that the prevalence of epilepsy in patients with autism was 12.1%, while the prevalence of autism in patients with epilepsy was 9.0%.[7] Taken together, these studies indicate that both the prevalence of autism

Received: 13 June 2022
Accepted: 14 September 2022
Published: 19 September 2022

in patients with epilepsy and the prevalence of epilepsy in patients with autism are higher than the reported rates of both disorders in the general population. At the same time, the prevalence of epilepsy/ASD shows a gradually increasing trend.

Epilepsy in patients with autism, or autism in patients with epilepsy, often exacerbates cognitive impairment and increases the risk of poor long-term prognosis. Although many studies suggest that epilepsy/ASD comorbidity may be related to genetics, metabolic disorders, infections, and other environmental influences, the details of the underlying mechanisms remain unclear.[11–13] In addition, there is still no effective diagnosis or treatment for epilepsy/ASD, which often depends on which disease occurs first; treatment is often provided according to clinical symptoms, resulting in a low diagnosis rate and poor treatment effects.[14,15] Therefore, it is necessary to summarize the history of the epilepsy/ASD research field and clarify its basis, current hotspots, and potential trends.

Bibliometrics is a quantitative method used to describe and analyze the dynamics and progress of a discipline or research field and to visualize the results of a literature analysis using correlation analysis software.[16,17] In the present study, we used the bibliometrics-related software applications VOSviewer and CiteSpace to perform bibliometric and visual analyses.[18,19] To the best of our knowledge, there is no existing bibliometric analysis of the epilepsy/ASD research field. To fill this gap, we conducted a quantitative analysis and visualization of cooperative networks (countries, institutions, and authors), published journals, co-citation references, keyword clustering, and keyword citation bursts in this research field. In doing so, our study systematically and objectively evaluates the basic, frontier, and hot topics in epilepsy/ASD research.

Methods

Data Sources and Search Strategies

As shown in Figure 1, data were retrieved using advanced search strategies in the Web of Science Core Collection (WoSCC), which is an extended version of the Science Citation Index. The following search terms were entered in the topic field: (“Epilepsy”

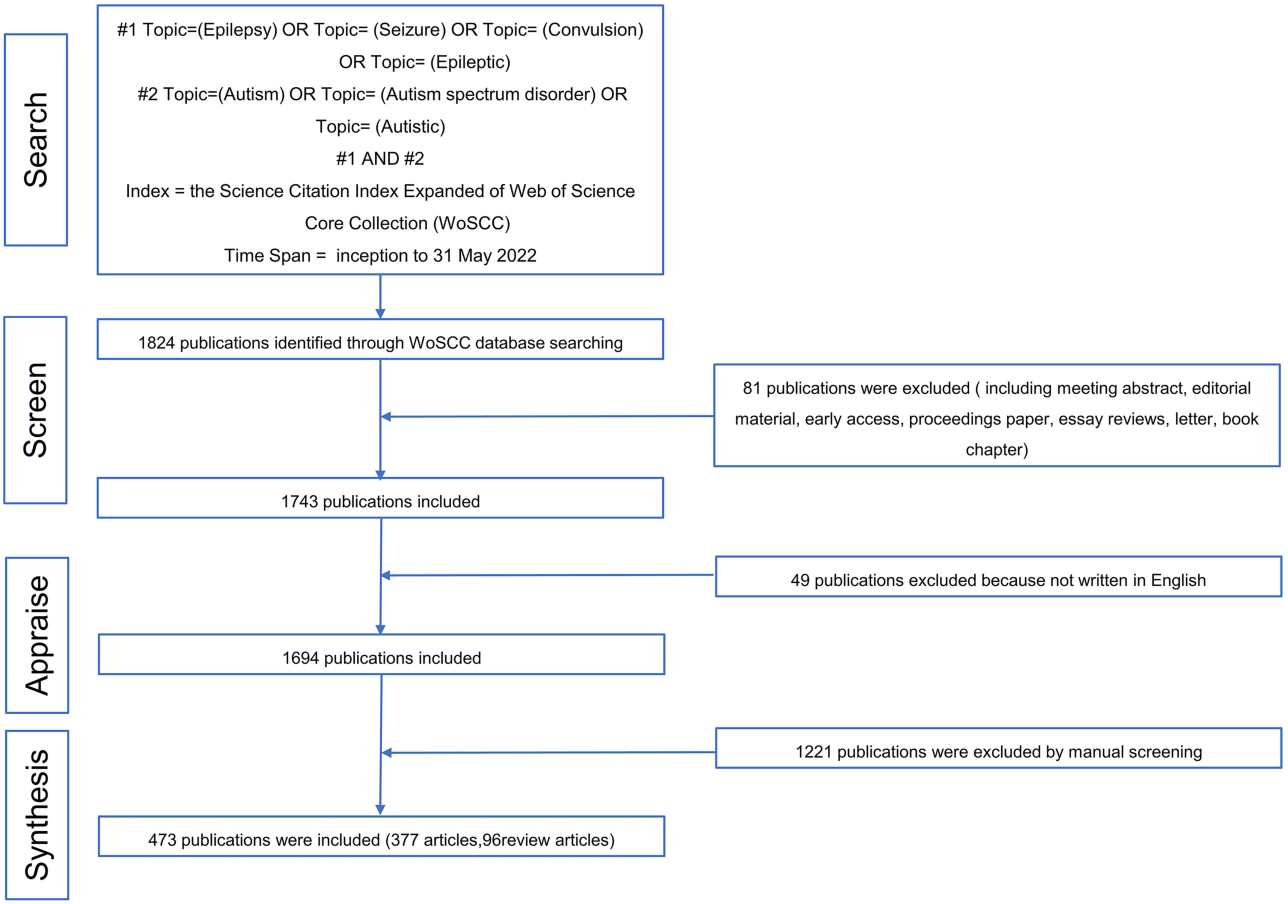

Figure 1 Flow chart of the literature screening process.

OR "Seizure" OR "Convulsion" OR "Epileptic") AND ("Autism Spectrum Disorder" OR "Autistic "OR" Autism") AND language = English. The time span for publication was from inception to 31 May 2022 and the document types were limited to original articles and reviews. In line with previous studies,[17,20] two independent researchers reviewed the titles and abstracts and excluded any studies unrelated to epilepsy/ASD. As a result, 473 publications were included in the subsequent analysis.

Data Analysis and Visualization

In this study, VOSviewer (version 1.6.18) and CiteSpace (version 6.1.R2) were used for bibliometric analysis and data visualization. First, we exported the records retrieved from WoSCC in plain text, including the full records and references, named download_XXX. txt. These data were then imported to VOSviewer and CiteSpace for bibliometric and visual analysis. VOSviewer is used to analyze countries, institutions, journals, co-authors, and co-citation references. CiteSpace identifies research fronts and emerging trends by analyzing annual publication numbers, growth trends, and co-occurring keywords clusters and capturing keywords with strong citation bursts over time.

Results

Bibliometric Analysis by Publication Year

As shown in Figure 2, 473 publications related to epilepsy/ASD were published from inception to 31 May 2022. The number of publications about epilepsy/ASD has generally increased over time, with some fluctuations. Prior to 2007, the number of publications was relatively small with no more than 10 publications published each year. From 2008 to 2014, the annual number of publications began to increase, achieving more than 20 publications in 2013. From 2015 to 2021, more than 30 articles were published each year. Sixty-two articles were published in 2020, which is the year with the most publications. As of 31 May 2022, 24 articles had been published that year.

Bibliometric Analysis of Journals

The 473 identified publications were published in 195 journals. First, journals with three or more epilepsy/ASD-related publications were visualized using VOSviewer (Figure 3). Next, we summarized the journals with the highest number of

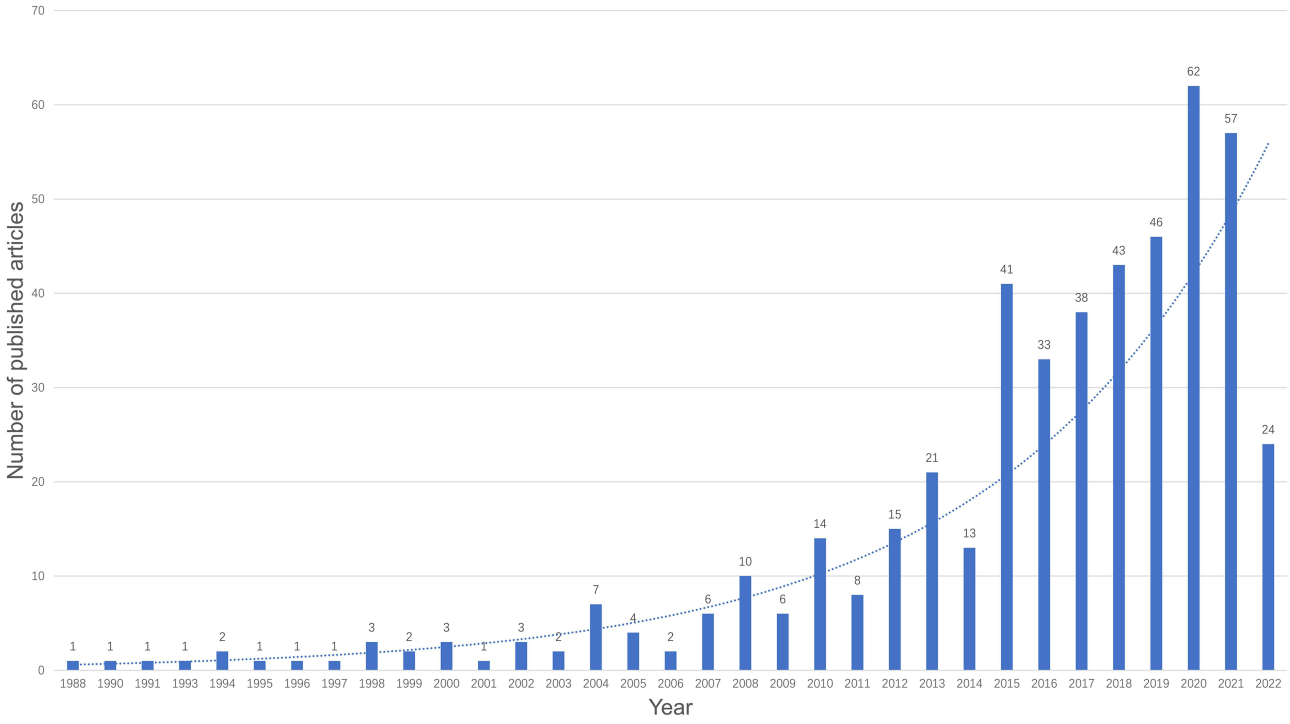

Figure 2 Annual trends in publications from inception to 31 May 2022.

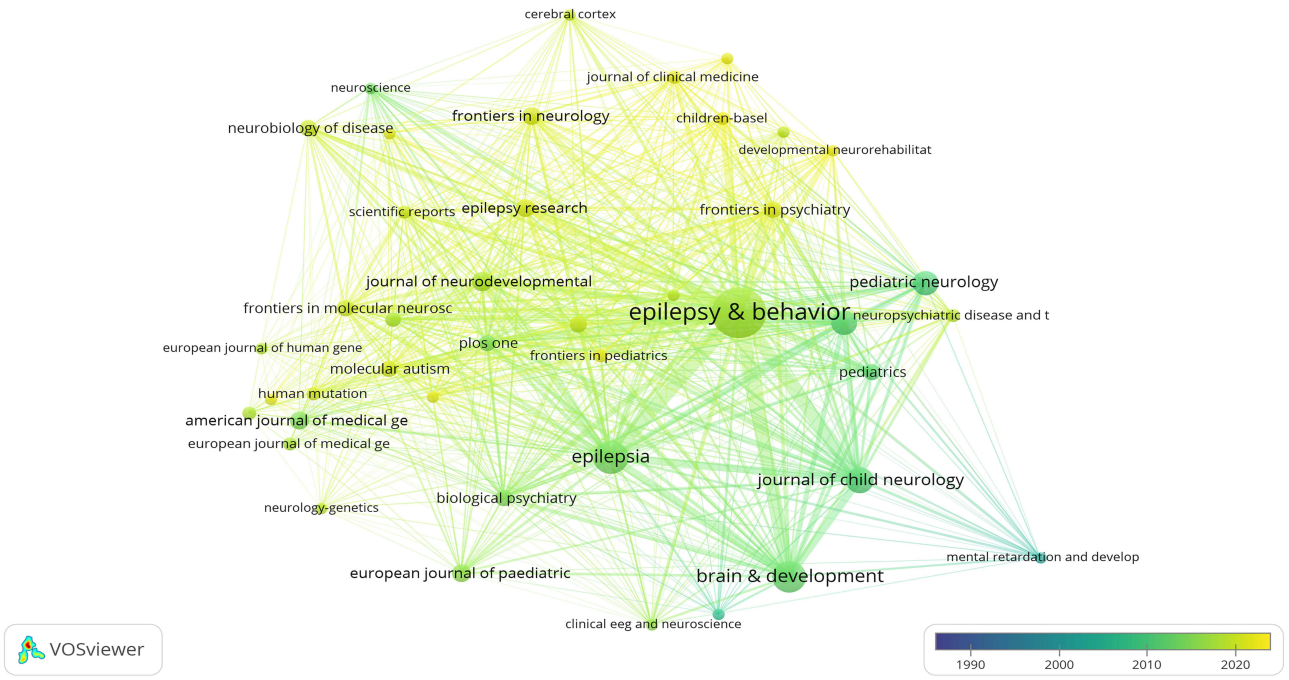

Figure 3 Visualization of the published journal network. The larger the node, the greater the volume of published articles. The node connection lines represent the strength of the relationship between journals. The color of the node represents the change in the number of published articles over time.

publications. Six journals published more than 10 papers each, together contributing a total of 114 papers (24.1%) (Table 1). The top three journals were *Epilepsy & Behavior* (46, 9.7%), *Epilepsia* (22, 4.7%), and *Brain & Development* (20, 4.2%).

Bibliometric Analysis of Countries and Institutions

The authors of the 473 publications analyzed in this study came from 55 countries and 1003 institutions. First, countries and institutions with six or more publications were visualized using Citespace (Figure 4). To further analyze high productivity countries and institutions, Table 2 presents the top five countries and institutions publishing epilepsy/ASD research. Together, these five countries published 388 papers (82%), and the country with the most publications was the USA (202, 42.7%). The number of publications from these five institutions totaled 63 (13.3%), and the institution with the most publications was the University of California-Los Angeles (15, 3.2%).

Bibliometric Analysis of Co-Authors

The 473 publications analyzed in this study had a total of 2584 authors. We visualized authors with three or more publications using VOSviewer (Figure 5). To explore what authors made the most significant contributions to epilepsy/ASD research, we summarized the authors with more than five publications (Table 3). The top three authors with the most publications were Frye, Richard E. (9, 1.9%), Gillberg, C (6, 1.3%), and Sahin, M (6, 1.3%).

Table 1 Journals with More Than 10 Publications in the Field of Epilepsy/ASD

Rank	Journal	Publications	Citations	Average Number of Citations per Publication
1	*Epilepsy & Behavior*	46	1026	22.3
2	*Epilepsia*	22	982	44.64
3	*Brain & Development*	20	1024	51.2
4	*Journal of Child Neurology*	14	452	32.29
5	*Developmental Medicine and Child Neurology*	12	788	65.67
5	*Pediatric Neurology*	12	476	39.67

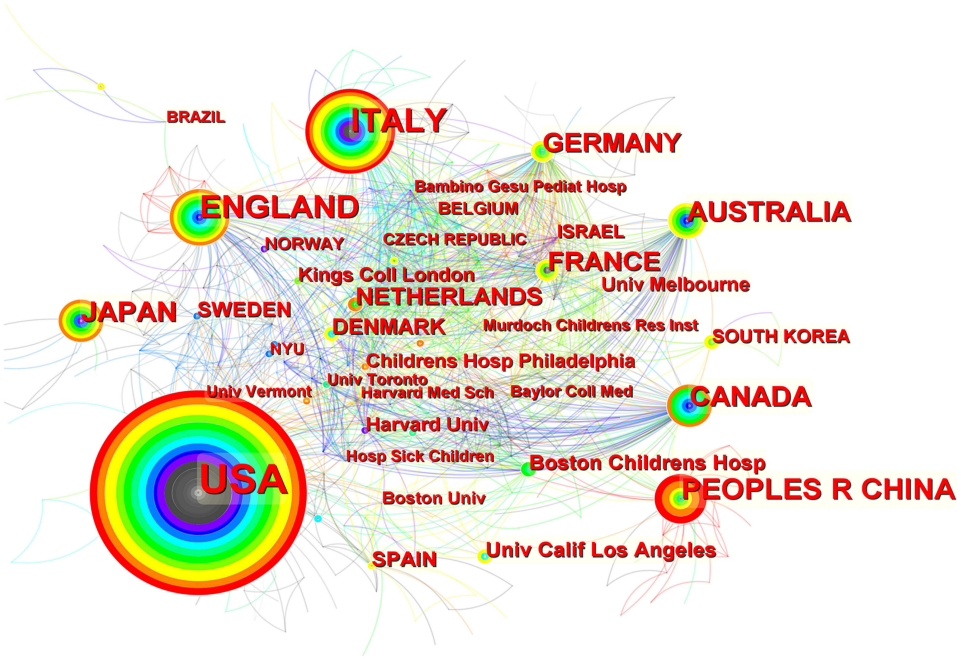

Figure 4 Network visualization of countries and institutions. The size of the colorful nodes represents the number of articles posted. The node connection lines represent the strength of the relationship between countries and institutions.

Bibliometric Analysis of Co-Cited References

A total of 18,017 references were co-cited in the 473 publications. Table 4 summarizes the 10 most cited references. The top three co-cited references were Tuchman R (2002) (65 citations), Amiet C (2008) (59 citations), Spence SJ (2009) (43 citations), and Volkmar FR (1990) (43 citations).

Bibliometric Analysis of Co-Occurring Keywords and Clusters

Table 5 lists the 10 most common keywords; autism spectrum disorder (frequency: 218), children (frequency: 132), epilepsy (frequency: 122), intellectual disability (frequency: 70), seizure (frequency: 62), prevalence (frequency: 54), spectrum disorder (frequency: 43), mutation (frequency: 35), gene (frequency: 33), mouse model (frequency: 32), and de novo mutation (frequency: 32). In CiteSpace, nodes with a centrality that exceeds 0.1 are called "key nodes". Therefore, Table 5 also summarizes keywords with centrality exceeding 0.1, namely children (centrality: 0.31), autism spectrum disorder (centrality: 0.25), epilepsy (centrality: 0.13), pervasive developmental disorder (centrality: 0.12), prevalence (centrality: 0.10), and spectrum disorder (centrality: 0.10).

We also used CiteSpace to perform cluster analysis of co-occurring keywords. We obtained 11 clusters. The average silhouette (S value) of the cluster is used as an indicator to evaluate clustering. Generally, $S > 0.5$ clustering is considered reasonable, while $S > 0.7$ means that clustering is convincing. Each of the obtained clusters has a silhouette value > 0.5,

Table 2 The Top Five Countries and Institutions Publishing Epilepsy/ASD Research

Rank	Country	Number of Publications	Rank	Institution	Number of Publications
1	USA	202	1	University of California-Los Angeles	15
2	Italy	60	2	University of Melbourne	14
3	England	53	3	Kings College London	12
4	China	41	4	Boston Children's Hospital	11
5	Canada	32	5	Harvard University	11

Figure 5 Network visualization of authors. The larger the node, the greater the number of published articles. The node connection lines represent the strength of the relationship between authors.

implying that the results are reasonable (Figure 6, Table 6). To gain further insight into the evolution of these clusters, we visualized the co-clustering timeline view using CiteSpace (Figure 7).

Bibliometric Analysis of Keywords with Citation Bursts

Lastly, we visualized the top 15 keywords with the strongest citation bursts (Figure 8). The blue line represents the time interval, while the red line represents the time period when the keyword bursts were found. The three most recent citation burst keywords occurred in 2019 (intellectual disability), 2020 (neurodevelopmental disorder), and 2020 (gene) and all lasted until 2022.

Table 3 Most Important Authors in the Epilepsy/ASD Research Field

Rank	Author	Number of Publications	Citations	Average Number of Citations per Publication
1	Frye, RE.	9	220	24.44
2	Gillberg, C	6	111	18.5
3	Sahin, M	6	199	33.17
4	Capal, JK	5	107	21.4
4	Scheffer, IE.	5	175	35
4	Scherer, SW.	5	111	22.2
4	Specchio, N	5	86	17.2
4	Trivisano, M	5	86	17.2
4	Tuchman, R	5	309	61.8

Table 4 The Top 10 Co-Cited References in the Epilepsy/ASD Research Field

Rank	Co-Cited References	Citations
1	Tuchman R,[31] 2002, lancet neurol, v1, p352, doi 10.1016/s1474-4422(02)00160–6	65
2	Amiet C,[10] 2008, biol psychiat, v64, p577, doi 10.1016/j.biopsych.2008.04.030	59
3	Spence SJ,[32] 2009, pediatr res, v65, p599, doi 10.1203/pdr.0b013e31819e7168	43
4	Volkmar FR,[33] 1990, j am acad child psy, v29, p127, doi 10.1097/00004583-199001000-00020	43
5	Danielsson S,[34] 2005, epilepsia, v46, p918, doi 10.1111/j.1528–1167.2005.57504.x	40
6	Hara H,[35] 2007, brain dev-jpn, v29, p486, doi 10.1016/j.braindev.2006.12.012	39
6	Viscidi EW,[36] 2013, plos one, v8, doi 10.1371/journal.pone.0067797	39
8	Chez MG,[37] 2006, epilepsy behav, v8, p267, doi 10.1016/j.yebeh.2005.11.001	35
8	Rossi PG,[38] 1995, brain dev-jpn, v17, p169, doi 10.1016/0387-7604(95)00019–8	35
10	Tuchman RF,[39] 1997, pediatrics, v99, p560, doi 10.1542/peds.99.4.560	33

Table 5 The Co-Occurrence Keywords of Epilepsy/ASD Research

Rank	Count	Keywords	Rank	Centrality	Keywords
1	218	Autism spectrum disorder	1	0.31	Children
2	132	Children	2	0.25	Autism spectrum disorder
3	122	Epilepsy	3	0.13	Epilepsy
4	70	Intellectual disability	4	0.12	Pervasive developmental disorder
5	62	Seizure	5	0.1	Prevalence
6	54	Prevalence	6	0.1	Spectrum disorder
7	43	Spectrum disorder			
8	35	Mutation			
9	33	Gene			
10	32	Mouse model			
10	32	De novo mutation			

Discussion

General Discussion

To the best of our knowledge, this is the first study to use VOSviewer and CiteSpace to review the field of epilepsy/ASD research and reveal research hotspots and frontiers. Our search of WoSCC identified a total of 473 articles that were published in 195 journals, cited a total of 18,017 references, and had a total of 2584 authors from 1003 institutions and 55 countries.

Based on our findings, the epilepsy/ASD research field can be roughly divided into three stages. From 1998 to 2007, researchers started to recognize epilepsy and autism comorbidities and the number of publications did not exceed 7 per year. From 2008 to 2014, researchers began to pay attention to epilepsy and autism comorbidities and the number of annual publications increased. Since 2015, there has been a rapid increase in the number of published papers. In 2020 and 2021 the number of published papers stabilized at more than 55 each year, indicating recent research attention. The rapid increase in the number of publications since 2015 may be due to several factors. First, the most recent diagnostic criteria for "autism spectrum disorder" in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) are more extensive, making the rate of ASD diagnosis increase.[11,21,22] Furthermore, awareness of the main behavioral symptoms of ASD, such as social impairment, communication difficulties, and stereotyped repetitive behaviors, has increased in general. Thus, although the prevalence of epilepsy has remained relatively stable, broader diagnostic criteria and better understanding of ASD have led to comorbid epilepsy/ASD receiving increased attention.[11]

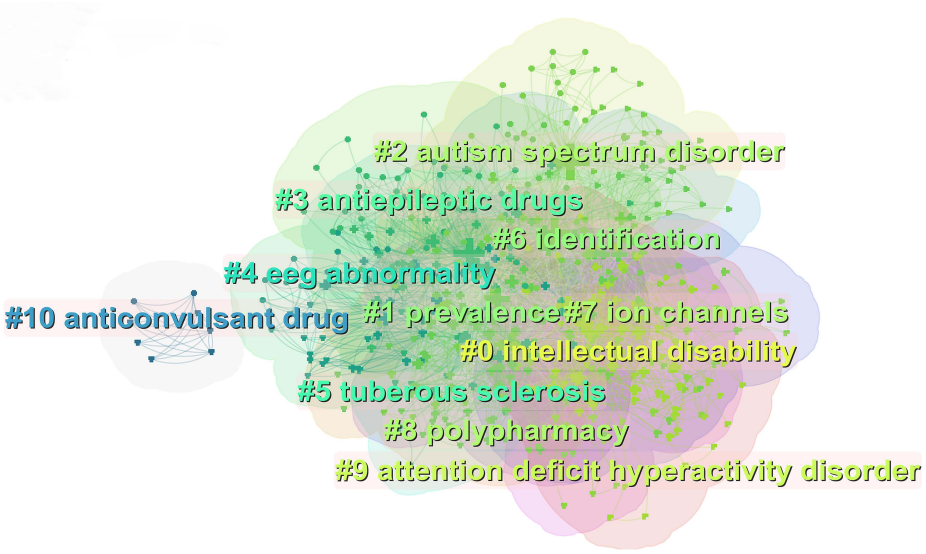

Figure 6 Visualization of the keywords cluster analysis.

Network

Journal Network

Although analysis of the journals in which epilepsy/ASD research are published cannot help us understand the current state of epilepsy/ASD research, nor can it predict future research trends, it can help us build theoretical foundations and submit high-quality articles. In the journal that published the most articles, *Epilepsy & Behavior*, recent articles include de novo *GRIN2A* variants associated with epilepsy and autism[23] and epilepsy in patients with focal cortical dysplasia that may be associated with ASD.[24]

Country and Institution Network

From inception to May 2022, the authors of the 473 publications came from 1003 institutions and 55 countries. The top five countries contributed 388 papers, accounting for 82% of all papers; the United States, which ranked first in terms of the number of papers, contributed 202. In addition, three of the top five institutions with the largest number of papers are

Table 6 Analysis of the Top 10 Clusters of Keywords in the Epilepsy/ASD Research Field

Cluster ID	Silhouette	Label	Included Keywords (Top 5)	Mean (Year)
0	0.636	Intellectual disability	Intellectual disability; mutation mouse model; de novo mutation; neurodevelopmental disorder;	2016
1	0.577	Prevalence	Seizure; prevalence; individual; pervasive; developmental disorder	2010
2	0.754	Autism spectrum disorder	Autism spectrum disorder; epilepsy; expression; animal model; cognitive impairment	2011
3	0.856	Antiepileptic drug	Children; Spectrum disorder; childhood; EEG; antiepileptic drug	2004
4	0.862	EEG abnormality	EEG abnormality; disorder; infantile autism; age; deficit	2002
5	0.799	Tuberous sclerosis	Tuberous sclerosis complex; infantile spasm; fragile x syndrome; childhood epilepsy; landau kleffner syndrome	2004
6	0.827	Identification	Gene; mental retardation; population; identification; association	2012
7	0.77	Ion channels	Autism; temporal lobe epilepsy; protein; variant; febrile seizure	2015
8	0.786	Polypharmacy	Adolescent; behavior; symptom; adult; anxiety	2014
9	0.796	Attention deficithyperactivity disorder	Brain; autism spectrum disorder (asd); adhd; attention deficit/hyperactivity disorder; double blind	2015

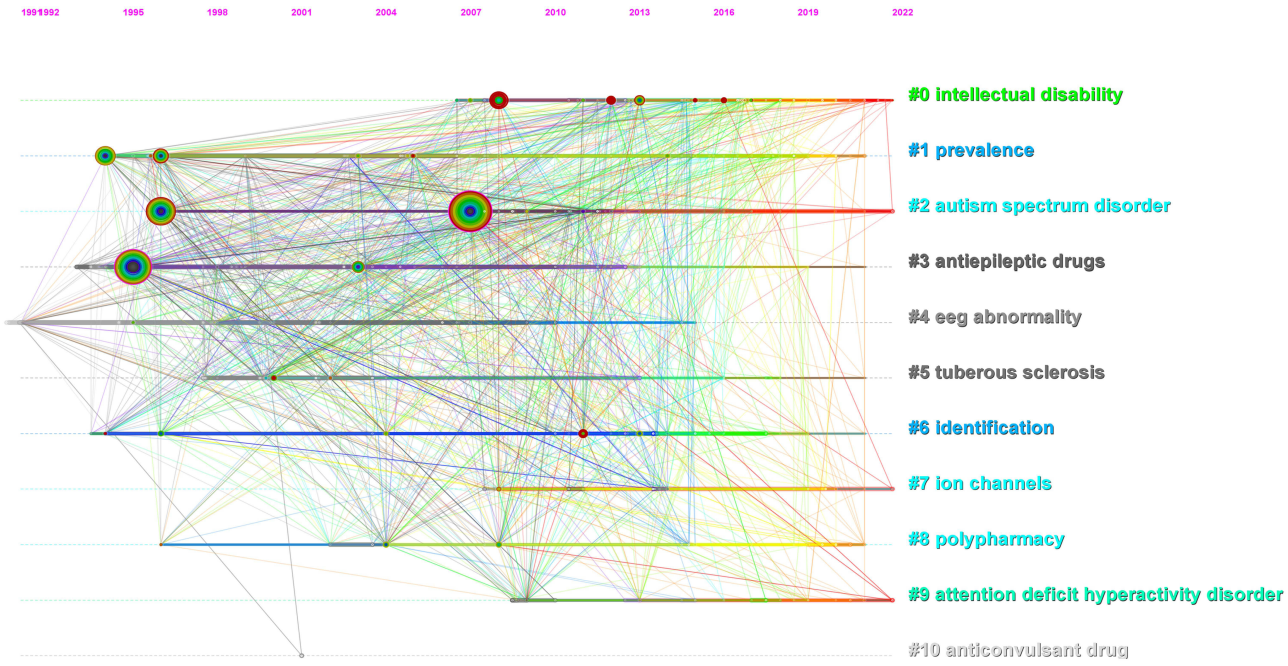

Figure 7 Co-clustering timeline view from 1988 to 2022. The node size and color indicate the total number of references and individual time slices, respectively. Different colored lines indicate that two articles are co-cited in one article. The solid line and dotted line correspond to clustering topics representing hot topics and non-hot topics, respectively, during the period.

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1988 - 2022
infantile autism	1988	5.38	**1991**	2009	
eeg	1988	3.94	**1993**	2011	
mental retardation	1988	4.65	**1994**	2016	
psychiatric disorder	1988	4.34	**1995**	2007	
childhood	1988	4.27	**1998**	2013	
landau kleffner syndrome	1988	3.62	**1998**	2004	
pervasive developmental disorder	1988	6.03	**1999**	2012	
tuberous sclerosis complex	1988	4.52	**2015**	2017	
risk	1988	4.3	**2015**	2016	
feature	1988	4.04	**2015**	2018	
de novo mutation	1988	4.27	**2016**	2020	
epileptic encephalopathy	1988	3.67	**2017**	2020	
intellectual disability	1988	6.5	**2019**	2022	
neurodevelopmental disorder	1988	4.9	**2020**	2022	
gene	1988	4.21	**2020**	2022	

Figure 8 The top 15 keywords with the strongest citation bursts.

from the United States. These results indicate that the distribution of countries publishing papers in this field is very uneven. Further progress in epilepsy/ASD research requires the participation and collaboration of more institutions and countries.

Author Network

Through analysis of the authors' collaborative network, we can identify representative scholars in the epilepsy/ASD research field. The author with the highest number of publications is Frye, R. E., who published recent articles discussing the pathogenesis of epilepsy and autism with topics such as metabolism, mitochondrial diseases, central nervous system metabolism, etc.[25–27] The author with the highest average number of citations per publication is Tuchman, R., who mainly discusses the relationship between epilepsy and ASD.[28–30] Although the number of authors of the 473 articles is as high as 2584, the author cooperation network map indicates that only a small number of authors cooperate closely and that most authors do not have cooperative relationships. This may constrain the development of epilepsy/ASD research.

Co-Cited References Network

By analyzing co-citation references, researchers can quickly grasp the basis of a research field. In the epilepsy/ASD field, the top 5 co-cited references were each cited more than 40 times. The most frequently cited publication is Tuchman, et al, which systematically expounded the relationship between epilepsy and autism.[31] The second most cited is Amiet, et al, which reported that the prevalence of epilepsy and autism comorbidity is related to intellectual disability and gender through meta-analysis.[10] Tied for the third most cited is Spence, et al, which elucidated the role of epilepsy and epileptiform electroencephalography in ASD,[32] and Volkmar, et al, which suggested that children with autism have the highest risk of seizures in early childhood.[33] The fifth most cited is Danielsson, et al, which elaborated the long-term outcome of epilepsy in autism and the epilepsy characteristics of adults with autism through prospective research.[34]

Hot Topics and Frontiers in Epilepsy/ASD Research

Keywords provide a core, high-level summary of an article. In bibliometrics, high frequency keywords are used to identify hotspots and frontiers in a research field. In this study, we summarized high frequency keywords, performed cluster analysis of these keywords, constructed a keyword clustering timeline graph, and finally analyzed keywords with citation bursts. Our results indicate that the keywords intellectual disability, neurodevelopmental disorder, gene, and mutation may represent hot topics and frontiers in epilepsy/ASD research.

Intellectual Disability

ID is a topic that cannot be avoided when people discuss the relationship between epilepsy and autism. As mentioned above, the second most co-cited reference is Amiet, et al, which found that the prevalence of epilepsy in autistic patients with ID was 21.5%, while the prevalence of epilepsy in autistic patients without ID was 8%.[10] With the deepening understanding of the relationship between epilepsy and autism, some studies suggest that ID may be a mediator between epilepsy and autism.[36,40–42] A recent study investigating the relationship between epilepsy, autism, and ID is Cogne, et al, which reported that missense variants in the histone acetyltransferase complex component gene *TRRAP* cause concurrent epilepsy, autism, and ID.[43] Brant, et al found that the *IQSEC2* mutation is associated with epilepsy, ID, and autism.[44] Although some scholars have suggested that clinical genetic sequencing of epilepsy/ASD patients with ID,[45] it must be admitted that the relationship between the three is unclear and it thus remains a clinical conundrum.[46] Therefore, more research is needed in the future to clarify the relationship between epilepsy, ID, and autism.

Genes, Mutation, and Neurodevelopmental Disorders

Although gene, mutation, and neurodevelopmental disorder appeared as three independent high frequency keywords or keywords with citation bursts in our analysis, in the actual publications we found that these three keywords often appeared together. From a genetic point of view, mutations can lead to neurodevelopmental

disorders, which in turn lead to a series of neurological diseases. Therefore, we explore these three keywords together in epilepsy/ASD research. Both epilepsy and autism are neurological disorders with multiple etiologies. However, thanks to advances in gene sequencing technologies and computational approaches, genetics has been shown to play a much greater role in epilepsy and autism than was previously appreciated. Therefore, when studying the underlying mechanism of epilepsy/ASD comorbidity, more and more researchers are adopting a genetic perspective. For example, Penagarikano et al confirmed that the absence of the *Cntnap2* gene can lead to epilepsy/ASD comorbidity by constructing animal models.[47] Stamberger et al[48] confirmed that *STXBP1* mutations can lead to STXBP1 encephalopathy, while Roston et al[49] showed that *SETD1B* mutations can lead to neurodevelopmental disorder, both of which may be risk factors for epilepsy/ASD comorbidity. Multiplex gene and phenotype networks have also been examined for a possible role in the pathogenesis of epilepsy/ASD comorbidity.[50] Many recent review articles have explored the mechanism of epilepsy/ASD comorbidity from a genetics perspective.[51–54] Based on our analysis and the above literature review, the three keywords gene, mutation, and neurodevelopmental disorder have gradually come to reflect hot spots and frontiers in the field of epilepsy/ASD research.

Limitations

This study is subject to several limitations. First, as our data only comes from the WoSCC database, our analysis may not be comprehensive enough. Second, our search was limited to original articles and reviews published in English, which makes the analysis incomplete to a certain extent. Finally, although VOSviewer and CiteSpace are professional bibliometric analysis software tools that provide objective analysis, since different researchers may have different views and interpretations of the same content, there may be some subjective bias.

Conclusion

The relationship between epilepsy and autism is extremely complex and the two conditions often co-occur, making it a challenging topic in both clinical and basic research. This study investigated the development of epilepsy/ASD research from its inception to 2022 through bibliometric analysis. Based on 473 articles obtained from WoS, we identified important publications, authors, journals, institutions, and countries and further analyzed the research network. Based on these findings, ID, which is an intermediary factor between epilepsy and autism, and exploring the mechanism of epilepsy/ASD from a genetics perspective are the main hotspot and frontier in this research field, respectively.

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.

Funding

Ningxia Brain plan-The basic and clinical research on tempo-insular neural network and brain recognizing functions (2002170101).

Disclosure

The authors report no competing interests in this work.

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