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Epilepsy-Specific Citation Classics Revisited

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With the exponential increase in peer-reviewed medical literature in recent decades, it is difficult to stay current in a field of expertise and easy to miss important articles. It is particularly challenging for those new to a field to become familiar with the existing body of scientific literature—the foundation on which future research and clinical paradigms are built. Given the large number of papers, evolving terminology and knowledge, and multidisciplinary nature of the field of epilepsy, it would be ideal to create a curriculum or reading list for trainees and new researchers. Citation frequency is one of several indicators that can be used to identify seminal articles that have had a significant scientific impact. The term "citation classic" was originally coined in a 1987 article in *JAMA* that identified and analyzed *JAMA*'s 100 most-cited articles in its history (1). Since that time, there have been numerous articles in a variety of fields that use bibliometrics to identify and analyze the most cited literature.

The purpose of this review is to identify and highlight "citation classics" in the epilepsy and seizure literature, defined as articles that have been cumulatively cited over 400 times. This review serves as a 5-year update to a 2012 article by Ibrahim et al. as published in *Epilepsia* (2). Our goals were to: 1) identify the most-cited articles relevant to epilepsy, which theoretically have had the highest impact; and 2) analyze trends in the literature that can indicate future directions of research.

Methods

To identify epilepsy-specific citation classics, we queried Scopus, the largest abstract and citation database of peer-reviewed literature, which includes scientific journal articles, books, and conference proceedings. Scopus was searched for all English language publications using the terms "epilep*" (inclusive of epilepsy, epileptic, epilepsies, and epilepticus) or "seizure*" (inclusive of seizure or seizures) in the title, abstract, or keywords. As in Ibrahim et al. (2), articles cited fewer than 400 times as sources in others' works were excluded from review. Two board-certified epileptologists (MK and DS) independently reviewed the title and abstract of each publication to determine if it was an epilepsy-specific or seizure-specific article, meaning that epilepsy or seizures were a central topic of study, discussion, or investigation. If there was any ambiguity or disagreement about the appropriateness of inclusion of an article, a third epileptologist and basic science researcher (GW) performed an independent review and contributed to the consensus decision. For example, a heavily cited review on multiple sclerosis mentioned rates of seizures in the MS population, but the article was excluded because it was not epilepsy specific; likewise, a review article entitled "Glutamate Uptake" was excluded because epilepsy and seizures were not the central theme of the review, despite discussion of certain antiepileptic drug (AED) mechanisms. Papers that discussed specific disease conditions or states were included if epilepsy was a central manifestation of the disease (e.g., Rasmussen syndrome, myoclonic epilepsy with ragged red fibers [MERRF] or NMDA receptor antibody encephalitis). Articles addressing mechanisms or efficacy of AEDs were also included.

The resulting citation classics were grouped into three broad categories: 1) human research, 2) animal research, and 3) reviews, guidelines, classification schemes, or consensus statements. This grouping differs slightly from that of Ibrahim et al., who defined the categories as 1) laboratory investigations, 2) clinical research, or 3) reviews or classification studies (2). We modified the categories because translational human research has been increasingly lab-based, particularly in genetics and neuroimmunology. As a check on our methodology, we ran a similar search strategy in Harzing's Publish or Perish (HPP) on April 5, 2017, the search method used by Ibrahim et al. HPP is an internet-based search engine that uses Google Scholar and Microsoft Academic data to calculate its citation metrics.

Finally, a qualitative analysis of the evolution of citation classics was undertaken, focusing on hot topics and methods by category over each decade. Due to the broad scope and frequent cross-disciplinary nature of epilepsy and seizure research—as well as incomplete key word indexing (especially for earlier studies)—a quantitative analysis of categories was not feasible. Pearson correlation coefficients were calculated to look for potential correlations between bibliometric "journal impact" scores (Scopus journal metrics, SJR, and CiteScore; 3) and number of publications or average citations per journal.

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FIGURE 1. Total English-language documents published over time (by year) that have the word fragments "seizure*" or "epilep*" in their title, abstract, or indexed key words.

Results

Search Results

Inclusion/Exclusion

The Scopus query was performed on February 2, 2017, and returned 236,810 English language publications (Figure 1). All articles with fewer than 400 citations were excluded from review, returning 680 publications for analysis. On preliminary independent review, the two clinical epileptologists (MK and DS) agreed that 130 (19.1%) were unequivocally epilepsy or seizure-specific, and 418 (61.5%) were eliminated for being clearly unrelated or only tangentially related to seizures or epilepsy. For the remaining 132 articles (19.4%) in which there was initial disagreement or uncertainty, a consensus agreement was reached after discussion between the two epileptologists and independent review by a third epileptologist and basic science researcher (GW) to determine the article's relevance to seizures or epilepsy.

Descriptive Statistics

A total of 185 articles (27.2% of the original 680) with over 400 citations were epilepsy or seizure-specific (see Appendix/Supplement 1 for complete list). This represents more than double the number of articles (n = 89) identified by Ibrahim et al. in 2012 using HPP. Eighteen articles had over 1,000 citations (Table 1), a nearly three-fold increase over the seven articles with greater than 1,000 citations in 2012. The average number of citations per article was 677 and the range was 400 to 4,592 (median = 532). The date of publication ranged from 1952 to 2011 (median = 1995). The articles were published in 56 different journals; the top 20 journals with two or more citations classics are listed in Table 2. The five journals that published the most epilepsy citation classics were *Epilepsia* (26 articles), *New England Journal of Medicine* (17), *Neurology* (13), *Science* (12), and *Brain* (11). There was no correlation between the total or average number of citation classics published per journal and the bibliometric "journal impact" scores of SJR or CiteScore for 2016 (Pearson correlation coefficients <0.15).

Categories

Of the 185 citation classics, 51 (27.6%) were categorized as reviews, classification systems, conference proceedings, and/or consensus statements. Over two-thirds (n = 134, 72.4%) represented primary clinical or laboratory research studies. Of these, 52 studies (28.1%) were animal-only investigations. The remaining 82 studies (44.3%) were clinical studies or primarily human investigations. However, at least five of the primarily human studies were based on genes or serum obtained from humans and then tested in animal models. Because the primary material tested was from human sources, we classified these five translational or applied research studies as human investigations.

Top Citation Classics

Of the 18 articles that were cited more than 1,000 times (Table 1), seven were reviews or consensus statements, six were animal-only investigations, and five were primarily human investigations. The most frequently cited article (4,592 citations) was a 1989 article, "A Proposal for Revised Classification of Epilepsies and Epileptic Syndromes: Commission on Classification and Terminology of the ILAE" from *Epilepsia* (4). The oldest of the top 18, published in 1972 (Racine), described "modification of seizure activity by electrical stimulation" (5), and the most recent from 2008 (Dalmau et al.), described "paraneoplastic anti-NMDA receptor encephalitis" (6).

Overall Trends in Citation Classics

The trends in numbers of citation classics in different categories over the decades are illustrated in Figure 2. The decade of the 1990s had the highest numbers of articles cited (1990–1999; 69 articles), followed by the 2000s (2000–2009;

TABLE 1. ***Top 18 Epilepsy-Specific Citation Classics (All Articles With >1,000 Citations)***

Current Rank	2011 Rank	Article	Current # Scopus citations	2011 # Publish or Perish Citations	Current # Google Scholar Citations
1	n/a	Proposal for revised classification of epilepsies and epileptic syndromes: Commission on classification and terminology of the international league against epilepsy. *Epilepsia* [Internet]. 1989;30:389–399.	4592	n/a	n/a
2	1	Racine RJ. Modification of seizure activity by electrical stimulation: II. Motor seizure. *Electroencephalogr Clin Neurophysiol* [Internet]. 1972;32:281–294.	4248	3749	5607
3	n/a	Proposal for revised clinical and electroencephalographic classification of epileptic seizures: From the commission on classification and terminology of the international league against epilepsy. *Epilepsia* [Internet]. 1981;22:489–501.	2805	n/a	n/a
4	n/a	Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* [Internet]. 1969;25:295–330.	2269	n/a	n/a
5	2	Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New Engl J Med* [Internet]. 2000;342:314–319.	2217	1419	3262
6	n/a	Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE commission on classification and terminology, 2005–2009. *Epilepsia* [Internet]. 2010;51:676–685.	1772	n/a	2671
7	10	Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *New Engl J Med* [Internet]. 2001;345:311–318.	1516	911	2091
8	5	Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* [Internet]. 1995;15:7539–7547.	1464	1193	1945
9	7	Engel J Jr.. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology. *Epilepsia* [Internet]. 2001;42:796–803.	1449	1123	2074
10	3	Ben-Ari Y. Limbic seizure and brain damage produced by kainic acid: Mechanisms and relevance to human temporal lobe epilepsy. *Neuroscience* [Internet]. 1985;14:375–403.	1379	1351	1702
11	6	Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* [Internet]. 1997;17:3727–3738.	1322	1162	1702
12	4	Morgan JI, Cohen DR, Hempstead JL, Curran T. Mapping patterns of c-fos expression in the central nervous system after seizure. *Science* [Internet]. 1987;237:192–196.	**1265**	**1303**	1657

TABLE 1. ***Top 18 Epilepsy-Specific Citation Classics (All Articles With >1,000 Citations)*** **Continued**

Current Rank	2011 Rank	Article	Current # Scopus citations	2011 # Publish or Perish Citations	Current # Google Scholar Citations
13	8	Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* [Internet]. 1993;34:453–458.	1210	996	1754
14	42	Fisher RS, Van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau For Epilepsy (IBE). *Epilepsia* [Internet]. 2005;46:470–472.	1162	525	2292
15	n/a	Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurol* [Internet]. 2008;7:1091–1098.	1128	n/a	n/a
16	12	Tanaka K, Watase K, Manabe T, Yamada K, Watanabe M, Takahashi K, Iwama H, Nishikawa T, Ichihara N, Kikuchi T, Okuyama S, Kawashima N, Hori S, Takimoto M, Wada K. Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. *Science* [Internet]. 1997;276:1699–1702.	1108	848	1381
17	n/a	Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. [Internet]. 1993;34:592–596.	1087	n/a	n/a
18	9	Shoffner JM, Lott MT, Lezza AMS, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNALys mutation. *Cell* [Internet]. 1990;61:931–937.	1022	961	1345

Current # Scopus citations = per methods and search performed on 2/2/17.
2011 # Publish or Perish citations = per results from original Ibrahim et al. article from supplementary material.
Current # Publish or Perish Google Scholar citations = per results from search performed 4/5/17.
Top 10 clinical, basic, reviews, "most relevant" 10.

TABLE 2A. ***Ranking of Journals in Which Epilepsy-Specific Citation Classics Are Published***

Current Rank	2011 Rank	Journal	# Citation Classics Published	2011 # Classics Published	Average # of Citations per Paper	SJR (2016)	CiteScore (2016)
1	1	*Epilepsia*	26	9	930	2.56	4.60
2	4b	*New England Journal of Medicine*	17	5	694	15.74	12.82
3	6c	*Neurology*	13	4	536	3.54	3.81
4	2a	*Science*	12	6	674	13.54	14.39
5	6d	*Brain*	11	4	537	5.47	7.31
6	6a	*Journal of Neuroscience*	9	4	695	4.68	5.96
7a	2b	*Nature Genetics*	8	6	670	20.90	20.83

TABLE 2A. ***Ranking of Journals in Which Epilepsy-Specific Citation Classics Are Published*** **Continued**

Current Rank	2011 Rank	Journal	# Citation Classics Published	2011 # Classics Published	Average # of Citations per Paper	SJR (2016)	CiteScore (2016)
7b	10	*Annals of Neurology*	8	3	599	5.34	7.10
9a	4a	*Nature*	5	5	558	18.13	13.33
9b	11g	*Lancet/The Lancet*	5	2	524	12.47	6.93
11a	6b	*Neuroscience*	4	4	713	1.69	3.42
11b	11d	*Proceedings of the National Academy of Sciences of the United States of America*	4	2	563	6.32	8.56
13a	11a	*Electroencephalography and Clinical Neurophysiology* (now *Journal of Clinical Neurophysiology*)	3	2	1834	0.67	1.42
13b	n/a	*The Lancet Neurology*	3		792	11.06	9.60
13c	19c	*Journal of Neurology, Neurosurgery and Psychiatry*	3	1	565	2.84	4.62
13d	11e	*Brain Research*	3	2	550	1.37	2.74
13e	11f	*Neuron*	3	2	523	11.12	11.13
13f	11h	*Nature Medicine*	3	2	509	14.21	14.43
19a	19l	*Experimental Neurology*	2	1	1338	2.28	4.40
19b	11b	*Cell*	2	2	805	27.70	23.62
19c	n/a	*Pharmacological Reviews*	2		787	8.90	18.92
19d	n/a	*Nature Reviews Neuroscience*	2		556	19.02	13.27
19e	19e	*Progress in Neurobiology*	2	1	525	5.84	13.28
19f	19i	*Neurosurgery*	2	1	479	1.31	1.38
19g	11c	*Archives of Neurology* (now *JAMA Neurology*)	2	2	470	4.21	5.10
19h	n/a	*Journal of Neurophysiology*	2		423	1.62	2.40
	Totals				**686.5**	**8.56**	**9.05**

TABLE 2B. ***Pearson Correlation Coefficients***

Calculation Between	Value
# Classics published (2016) and Avg # Cit per paper	0.0426993
# Classics published (2016) and SJR (2016)	–0.0282496
# Classics published (2016) and CiteScore (2016)	–0.055463
Avg # Cit per paper and SJR (2016)	–0.1647134
Avg # Cit per paper and CiteScore (2016)	–0.1386953
SJR (2016) and CiteScore (2016)	0.8812968

54 articles), and the 1980s (1980–1989; 33 articles). An earlier publication date allows more opportunities for citation, thus, the peak citation classics tended to be published at least 10 years prior to the query date. However, because there has been a marked increase in the number of peer-reviewed publications over the last 30 years, more recent hot articles (such as the 2008 Dalmau et al. article) get more current exposure and thus increased likelihood of new citations. As knowledge and technology evolve, the hot topics and methods in research also evolve. Table 3 lists the Top Ten citation classics in each category and the most recent ten articles with greater than 400 citations.

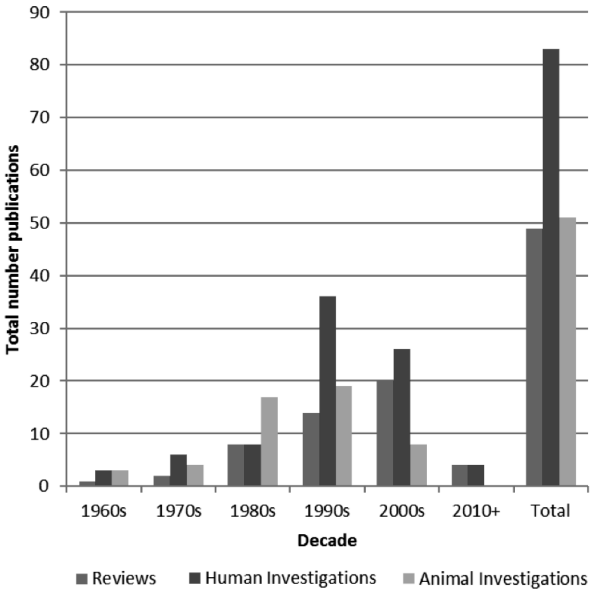

FIGURE 2. Trends in categories of epilepsy-specific Citation Classics over time.

Trends in Human Research

The earliest citation classic in the human research category is Landau's seminal 1957 article describing Landau-Kleffner syndrome (7). In the 1960s, two of the three human research articles were case series describing psychosis and mood disorders in epilepsy (8, 9), and the remaining article described temporal lobe epilepsy (TLE) pathology, EEG, and clinical presentation (10). In the 1970s, four of the six human research studies involved the epidemiology of epilepsy and the natural history of the disease (11–14); two of the four were focused on febrile seizure prognosis. The remaining two studies from the 1970s explored interictal behavior in TLE and focal cortical dysplasia in epilepsy (15, 16). In the 1980s, the first multicenter randomized controlled trial (RCT) for epilepsy therapy was published comparing the efficacy and toxicity of four established AEDs (17). Other human investigation articles focused on cortical stimulation mapping (2 articles), neuropathology in TLE (2 articles), and natural history studies (2 articles) of dysembryoplastic neuroepithelial tumors (DNETs) and febrile seizures. One novel article performed time series computational analysis of human EEG to model the dynamic state of seizures using chaos theory (18).

The 1990s witnessed a marked increase in citations classics involving human investigations in epilepsy, which surpassed the number of animal studies (36:19 articles). Six RCTs were published, including the first surgical trial of vagal nerve stimulation (19). The other five RCTs tested AEDs for specific subsets of seizures: posttraumatic seizures, complex partial seizures, new diagnosis of epilepsy, pre-eclampsia, and convulsive status epilepticus. The 1990s also included rapid advances in genetic studies that included the characterization of genes involved in epilepsy syndromes as documented in five landmark articles: 1) benign familial neonatal convulsions, 2) febrile seizures, 3) progressive myoclonic epilepsy Type 1, 4) myoclonic epilepsy and ragged-red fiber disease, and 5) certain idiopathic generalized epilepsies (KQT, GEFS+). Additionally, the decade witnessed marked advances in neuroimaging of epilepsy; hence, three articles described different imaging techniques: MRI with hippocampal volume analysis, functional MRI for language, and positron emission topography (PET) in infantile spasms. In human research studies, natural history and epidemiology studies were the most numerous subgroup (14/36 articles), and there were three studies looking at molecular and cellular anatomy and neurophysiology of the human hippocampus. A pioneering study proposed an autoantibody-medi-

TABLE 3. ***Top 10 Citation Classics by Category***

Rank	First Author	Journal	Title	Year	# Total Citations	# Cit/year
a) Clinical investigations						
1	Kwan P	*NEJM*	Early identification of refractory epilepsy	2000	2217	130.4
2	Wiebe S	*NEJM*	A randomized, controlled trial of surgery for temporal-lobe epilepsy	2001	1516	94.8
3	Hauser W	*Epilepsia*	Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984	1993	1210	50.4
4	Dalmau J	*Lancet Neurology*	Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies	2008	1128	125.3
5	Shoffner J	*Cell*	Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNALys mutation	1990	1022	37.9
6	Ojemann G	*J Neurosurg*	Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients	1989	909	32.5

TABLE 3. ***Top 10 Citation Classics by Category*** **Continued**

Rank	First Author	Journal	Title	Year	# Total Citations	# Cit/year
7	Margerison J	*Brain*	Epilepsy and the temporal lobes: A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes	1966	893	17.5
8	Mattson R	*NEJM*	Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures	1985	886	27.7
9	Wallace R	*Nature Genetics*	Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel beta1 subunit gene *SCN1B*	1998	818	43.1
10	Hauser W	*Epilepsia*	The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967	1975	806	19.2
b) Animal investigations						
1	Racine R	*EEG & Clin Neurophys*	Modification of seizure activity by electrical stimulation: II. Motor seizure	1972	4248	94.4
2	Goddard G	*Experimental Neurology*	A permanent change in brain function resulting from daily electrical stimulation	1969	2269	47.3
3	Nibuya M	*J Neurosci*	Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments	1995	1464	66.5
4	Parent J	*J Neurosci*	Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus	1997	1322	66.1
5	Morgan J	*Science*	Mapping patterns of c-fos expression in the central nervous system after seizure	1987	1265	42.2
6	Tanaka K	*Science*	Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1	1997	1108	55.4
7	Gee N	*J Bio Chem*	The novel anticonvulsant drug, gabapentin (neurontin), binds to the alpha2delta subunit of a calcium channel	1996	876	41.7
8	Sloviter R	*Science*	Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy	1987	756	25.2
9	Tauck D	*J Neurosci*	Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats	1985	754	23.6
10	Krall R	*Epilepsia*	Antiepileptic drug development: II. Anticonvulsant drug screening	1978	741	19
c) Reviews, consensus and definition statements						
1	NL	*Epilepsia*	Proposal for revised classification of epilepsies and epileptic syndromes	1989	4592	164
2	NL	*Epilepsia*	Proposal for revised clinical and electroencephalographic classification of epileptic seizures	1981	2905	77.9
3	Berg A	*Epilepsia*	Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009	2010	1772	253.1

TABLE 3. ***Top 10 Citation Classics by Category*** **Continued**

Rank	First Author	Journal	Title	Year	# Total Citations	# Cit/year
4	Engel J	*Epilepsia*	A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology	2001	1449	90.6
5	Ben-Ari Y	*Neuroscience*	Limbic seizure and brain damage produced by kainic acid: Mechanisms and relevance to human temporal lobe epilepsy	1985	1379	43.1
6	Fisher R	*Epilepsia*	Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)	2005	1162	96.8
7	NL	*Epilepsia*	Guidelines for epidemiologic studies on epilepsy	1993	1087	45.3
8	Perez-Reyes E	*Physiological Reviews*	Molecular physiology of low-voltage-activated T-type calcium channels	2003	985	70.4
9	Pacher P	*Pharmacological Reviews*	The endocannabinoid system as an emerging target of pharmacotherapy	2006	977	88.8
10	Kwan P	Epilepsia	Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies	2010	865	123.6
d) Most recent publications (in order of number citations)						
1	Berg A	*Epilepsia*	Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009	2010	1772	253.1
2	Kwan P	*Epilepsia*	Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies	2010	865	123.6
3	Dalmau J	*Lancet Neurology*	Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis	2011	815	135.8
4	Blumcke I	*Epilepsia*	The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission	2011	575	95.8
5	Fisher R	*Epilepsia*	Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy	2010	548	78.3
6	Florance N	*Annals Neurology*	Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents	2009	482	60.3
7	Vezzani A	*Nature Reviews Neurology*	The role of inflammation in epilepsy	2011	455	75.8
8	Lai M	*Lancet Neurology*	Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: A case series	2010	434	62
9	Irani S	*Brain*	N-methyl-d-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes	2010	431	61.6
10	Meador K	*NEJM*	Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs	2009	404	50.5

ated mechanism for Rasmussen's disease pathophysiology (20), although the antibody described (GluR3) was ultimately found not to be the pathological agent. Of note, two articles in the 1980s tested human genes or serology in animal models (20, 21), representing some of the earliest translational human–animal investigations.

Since 2000, the newer "hot topics" of human research have included neuroinflammation and autoantibodies (6 articles), AED teratogenicity and effects on neurodevelopment (2 articles), ICU EEG prognostication (2 articles), and computational neuroscience studies looking at dynamic systems and synchronization in EEG (2 articles). As in the 1990s, there were numerous citation classics in genetics (4 articles), treatment RCTs (5 articles), and epidemiological and natural history studies (5 articles). By contrast, only 1 classic examined the molecular and cellular pathophysiology of human temporal lobe epilepsy (22), a more common topic in prior decades. The three most recent highly cited human investigation studies (published in 2010) examined the temporal progression of NMDA antibody encephalitis (23), LGI1 as an antigen in limbic encephalitis (24), and the RCT of thalamic deep brain stimulation for the treatment of epilepsy (25).

Trends in Animal Research

The earliest citation classic in the animal research category is Swinyard's "Comparative Assays of Antiepileptic Drugs in Mice and Rats," published in 1952 (26). In the 1960s, the three animal research articles included Goddard's electrical stimulation studies (27, 28) and a seminal article concerning the paroxysmal depolarizing shift in a feline penicillin model of epilepsy (29). In the 1970s, the four animal research articles were Racine's seminal papers on the modification of seizure activity by electrical stimulation (5, 30), an article on AED drug development by molecule screening at the NINDS (31), and an influential paper on the kainic acid model of epilepsy (32).

The 1980s was the only decade in which the number of citation classics involving animal research outnumbered human investigations (ratio 17:8). The most common methods from that decade were molecular and cellular neuroanatomy and neurophysiology investigations, the majority involving the hippocampus (12 of the 17 articles). The most common topics of the 1980s included animal models of epilepsy (kainic acid [4], pilocarpine [1], and kindling [2]); electrical stimulation studies (3 articles); and mechanisms of action (4 articles) of novel AEDs (lamotrigine) and other molecules (GABA, amino acids, magnesium). Later in the decade, there were two seminal studies describing gene expression alterations with seizures (c-fos protein and nerve growth factor).

In the 1990s, animal research remained heavily focused on molecular and cellular neuroanatomy and neurophysiology, the majority involving the hippocampus (10 of the 19 articles). Animal models remained a common theme, particularly the models using kindling (5 articles), pilocarpine (3 articles), and fluid-percussion injury (1 article, to model the effect of TBI). Over the decade, there were increasing studies of genetic expression (GLT1, TPA, BDNF) and neurotransmitter receptor regulation (GABA, NMDA, calcium channels). There were several important papers on the neurophysiological basis for EEG findings, including spindles and spike-wave discharges (33, 34).

Since the year 2000, only eight exclusively animal investigation studies have been cited over 400 times. The most recent article, published in 2006, was entitled "Reduced Sodium Current in GABAergic Interneurons in a Mouse Model of Severe Myoclonic Epilepsy in Infancy" by Yu et al. (35) highlighted the direction much laboratory research has taken: translational or applied research. Similarly, two of the eight studies used knock-out mouse models (genes *Sma1*, *Ampa*) to examine the pathophysiological effects of loss or alteration of function (36, 37). Two articles described novel mechanisms of action of newer drugs (levetiracetam and bumetanide; 38, 39). Two articles examined the pathophysiological basis for neurogenesis after seizures, (40, 41) and one article implicated astrocytes in epilepsy pathogenesis (42).

Trends in Review Articles, Classification, and Consensus Statements

In general, the topics of review articles mirrored the evolution of the human and animal investigations work described above. In the 1960s through the 1970s, temporal lobe epilepsy and kindling were topics of heavily cited reviews. In the 1980s, animal model reviews were most highly cited (five articles), AED drug development was reviewed by the NINDS Epilepsy Branch (43), and the first two ILAE definitions and consensus statements were published (4, 44) in 1981 and 1989. By the 1990s, the highly cited review topics were quite varied. Over time, there have been an increasing number of consensus statements and guidelines highly cited: two in the 1980s, three in the 1990s, six from 2000 through 2009, and three from 2010 to the present.

Discussion

The rationale for this paper is to help establish the canon of epilepsy and seizure literature, identify trends in research over time, and examine trends in the epilepsy literature in the 5 years since the original epilepsy citation classics article. The citation classics arguably represent some of the most influential work in the field of seizures and epilepsy. Alternatively, they may represent a sample of the more "useful" articles, which are cited more because they describe a certain technique, model or terminology commonly used in subsequent research (e.g., animal models, ILAE consensus statements).

Some argue that the total number of citations is not a good indicator of article importance, since it favors older articles that have had more time to accumulate citations. An alternative method used for determining current or "trending" articles is number of citations divided by number of years since publication, thus highlighting articles that have had the most citations per year. This method favors identifying newer or hotter articles that may not ultimately be considered classics over time. A recent bibliometric analysis of the neurosurgical literature by Bohl et al. used cumulative citations in one paper to identify "citation classics" or "foundational papers in neurosurgery," whereas they used average citations per year in a separate paper to identify "the most *relevant* papers in neurosurgical journals" (45, 46; emphasis added). Our analysis chose focus on cumulative citations because these articles have proven the test of time.

Regardless of the search strategy, noting the trends in the most highly cited articles over the decades informs the evolu-

tion of our understanding of seizures and epilepsy. As the number of highly cited articles grows, the definition of a "citation classic" as one that has more than 400 citations may need to be updated. Nevertheless, the trends identified in the evolution of the epilepsy and seizure literature have typically followed the general scientific trends in medicine and basic neuroscience. Some salient trends identified included the 1) predominance of molecular and cellular pathophysiology studies in the 1970s to the 1990s, 2) the increasing influence of genetic studies from the 1990s to present, 3) the recent focus on neuroinflammation over the last decade, 4) the steady increase in multicenter RCTs and translational or applied research over recent decades, and 5) the increase in guidelines and consensus statements over recent decades.

Bibliometrics, defined as the statistical analysis of written publications, is an evolving field in which multiple databases and search engines can be used to identify and analyze trends in the scientific literature. We selected Elsevier's online subscription-based Scopus as our query tool because Scopus is the largest abstract and citation database of peer-reviewed literature, including scientific journals, books, and conference proceedings. Additionally, the Scopus collection is curated and updated daily by librarians and researchers who ensure that only adequately peer-reviewed journals are included.

Our methodology differs from the original epilepsy citation classic article by Ibrahim et al. (2), which used Harzing's Publish or Perish (HPP) to identify the top-cited articles. Unlike Scopus, HPP is a free software program that uses Google Scholar and Microsoft Academic Search to obtain the raw citations, which are not necessarily peer-reviewed and are not curated by librarians and scientists. HPP processing is automatic (unlike Scopus, which involves manual handling and checking by medical librarians, with the associated increased cost); hence, occasional errors or omissions do occur. Another limitation of HPP is that it can access only references that are available online; due to publisher policies, it does not have access to a substantial number of journals. Given these methodological differences, there are differences in numbers of citations between the different indexing services at different times, as illustrated in Table 1. Consistently, higher numbers of citations are indexed by Google Scholar when compared to Scopus because of these methodological differences. Additionally, four of the ten top-cited articles in our analysis were not listed in Ibrahim's top articles, whereas one of the four was identified by a current Google Scholar query (47), and three others were not identified by Google Scholar (4, 27, 44). Two of the three articles identified by Scopus but not Google Scholar were consensus statement articles from the ILAE on epilepsy and seizure classification and terminology, and one was Goddard's seminal article on kindling from daily electrical stimulation.

A recent article by Park et al. analyzed publications that addressed epilepsy and status epilepticus, with methodology that differed from our current approach and that of Ibrahim et al. (48). First, Park et al. used different search terms of "epilepsy" and "status epilepticus" (not inclusive of "seizure") and used Web of Science as their bibliometric search engine; they then limited their article inclusion to those published journals with three subject categories: "clinical neurology" (192 journals), "neuroscience" (252 journals), and "medicine, general & internal" (110 journals) before reviewing the articles manually. The different query approaches led to different results. For example, our search method identified all of Park's ten top-cited epilepsy articles, but Park's method failed to identify six of our top ten (three of which were ILAE consensus articles [4, 44, 47] and three were basic science electrophysiology articles [5, 27, 49]). Additionally, the number of citations identified using Scopus was usually more than double those identified using Web of Science—too large a difference than can be explained by performing the queries one year apart.

The different results amongst the "top cited" epilepsy articles highlight the imperfect nature of bibliometric analysis. By choosing slightly different search terms, including or excluding certain references (e.g., particular journals that refuse indexing or are not peer-reviewed), or searching at different times, the results can be drastically different. Moreover, our analysis found no significant correlations between "journal impact" factors such as Scopus's SJR or CiteScore[3] and number of citation classics published or average number of citations per article published. These measures use proprietary algorithms to rate how highly cited or prestigious a journal is using methods that vary between companies calculating such measures.

The strengths of our study are that we used a comprehensive peer-reviewed database with the assistance of a librarian trained in bibliometrics, and all the abstracts were reviewed by two to three board-certified epileptologists to determine the relevance to seizures and epilepsy. The limitations of the study are that while there was simple consensus on the relevance or irrelevance of majority of the articles, there was initial uncertainty or disagreement regarding the relevance of 132 (19.4%) of the 680 studies identified in the Scopus query. For example, our team chose to include NMDA receptor encephalitis as a relevant disease entity since seizures are a salient feature and chronic epilepsy is common sequelae; however, different authors or investigators may have chosen to exclude NMDA encephalitis studies as a separate entity like multiple sclerosis. To minimize this potential bias, a third investigator served as mediator for articles on which there was initial uncertainty. Although frequency of citations is the common currency in academic science, the idea that it reliably identifies the most important articles in a field has been questioned. Specifically, not all citations are equal, and other methods have been proposed (50). Because we used a different search method than did prior investigators, our results cannot be directly compared. Finally, our ability to identify salient research topics, methods, and trends over time was limited to a qualitative description because key words indexed were not uniform and were often absent, particularly in earlier years.

Our search strategy readily identified relevant clinical articles that contained the target search terms in the title or abstract. However, this strategy may less reliably identify relevant basic science articles that do not specifically address seizures and epilepsy yet are fundamental to our understanding of these conditions. Examples range from articles outlining the physics of MRI to papers that establish our understanding of cell membrane and receptor properties that drive bursting and excitability in seizures. Thus, the identified citation classics likely underestimate the profound basic science contributions to our current and future understanding of epilepsy.

Conclusion

Our results identified top-cited articles in the epilepsy and seizure literature, updating and expanding upon previous studies using different search methods. This is the first bibliometric analysis of the epilepsy and seizure literature to chronicle the trends in "hot topics" and research methods over time and by category. Through chronological analysis, the salient trends identified included the 1) predominance of molecular and cellular pathophysiology studies in the 1970s to the 1990s, 2) increase in genetic studies from the 1990s to present, 3) the recent focus on neuroinflammation over the last decade, 4) the steady increase in multicenter RCTs and translational or applied research over time, and 5) the increase in guidelines and consensus statements over recent decades.

Although helpful to identify general trends and most relevant highly cited works, we identified some of the limitations and challenges of bibliometric analysis of scientific publications in a given field. Slightly different methods and search queries at different times can yield drastically different results, and bibliometric search engines use proprietary, opaque algorithms so their results cannot be directly compared and validated. Finally, bibliometric analysis still requires manual review of the publications to ensure their relevance to the analysis; therefore, these methods remain prone to human error and differences in opinion. These limitations notwithstanding, these are the primary tools currently available to winnow the ever-increasing body of scientific literature and identify sentinel articles that form the foundation of our current knowledge.

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References

1. Garfield E. 100 citation classics from the *Journal of the American Medical Association. JAMA* 1987;257:52–59.
2. Ibrahim GM, Carter Snead O, Rutka JT, Lozano AM. The most cited works in epilepsy: Trends in the "citation classics." *Epilepsia* 2012;53:765–770.
3. Journal Metrics. Scopus.com. https://journalmetrics.scopus.com/. Accessed August 23, 2017.
4. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–399.
5. Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalogr Clin Neurophysiol* 1972;32:281–294.
6. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurol* 2008:7:1091–1098.
7. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. *Neurology* 1957:7:523–530.
8. Slater E, Beard AW, Glithero E. The schizophrenialike psychoses of epilepsy. *Br J Psychiatry J Ment Sci* 1963;109:95–150.
9. Flor-Henry P. Psychosis and temporal lobe epilepsy; A controlled investigation. *Epilepsia* 1969;10:363–395.
10. Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes: A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain* 1966;89:499–530.
11. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 1975;16:1–66.
12. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. *Pediatrics* 1978;61:720–727.
13. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. *N Eng J Med* 1976:295:1029–1033.
14. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979:20:729–737.
15. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. *J Neurol Neurosurg Psychiatry* 1971:34:369–387.
16. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch Neurol* 1977:34:454–467.
17. Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB, Homan RW, Crill WE, Lubozynski MF, Rosenthal NP, Mayersdorf A. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. *N Engl J Med* 1985:313:145–151.
18. Babloyantz A, Destexhe A. Low-dimensional chaos in an instance of epilepsy. *Proc Natl Acad Sci U S A* 1986;83:3513–3517.
19. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW. Vagus nerve stimulation therapy for partial-onset seizures: A randomized active-control trial. *Neurology* 1998:51:48–55.
20. Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, Hughes TE, Heinemann SF, McNamara JO. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. *Science* 1994;265:648–651.
21. Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, Steinlein OK. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403–406.
22. Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. *Science* 2002;298:1418–1421.
23. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese MA, Galea I, Kullmann DM, Beeson D, Lang B, Bien CG, Vincent A. N-methyl-D-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain J Neurol* 2010;133:1655–1667.
24. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, Cowell JK, Dalmau J. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: A case series. *Lancet Neurol* 2010:9:776–785.
25. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51:899–908.
26. Swinyard EA, Brown WC, Goodman LS. Comparative assays of antiepileptic drugs in mice and rats. *J Pharmacol Exp Ther* 1952:106:319–330.

27. Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. *Nature* 1967;214:1020–1021.
28. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* 1969:25:295–330.
29. Matsumoto H, Marsan CA. Cortical cellular phenomena in experimental epilepsy: Interictal manifestations. *Exp Neurol* 1964;9:286–304.
30. Racine RJ. Modification of seizure activity by electrical stimulation: I. After-discharge threshold. *Electroencephalogr Clin Neurophysiol* 1972;32:269–279.
31. Krall RL, Penry JK, White BG, Kupferberg HJ, Swinyard EA. Antiepileptic drug development: II. Anticonvulsant drug screening. *Epilepsia* 1978;19:409–428.
32. Nadler JV, Perry BW, Cotmon CW. Intraventricular kainic acid preferentially destroys hippocampal pyramidal cells. *Nature* 1978;271:676–677.
33. Von Krosigk M, Bal T, McCormick DA. Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 1993:261:361–364.
34. Letts VA, The mouse stargazer gene encodes a neuronal $Ca2^{+}$-channel gamma subunit. *Nat Genet* 1998;19:340–347.
35. Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat Neurosci* 2006;9:1142–1149.
36. Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS, Nicoll RA. Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* 2000;408: 936–943.
37. Meeren HKM, Pijn JPM, Van Luijtelaar ELJM, Coenen AML, Da Silva FHL. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *J Neurosci* 2002;22:1480–1495.
38. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B. The synaptic vesicle is the protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A* 2004;101:9861–9866.
39. Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, Delpire E, Jensen FE, Staley KJ. NKCC1 transporter facilitates seizures in the developing brain. *Nat Med* 2005;11:1205–1213.
40. Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingström A. Increased neurogenesis in a model of electroconvulsive therapy. *Biol Psychiatry* 2000;47:1043–1049.
41. Scharfman HE, Goodman JH, Sollas AL. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: Functional implications of seizure-induced neurogenesis. *J Neurosci* 2000;20:6144–6158.
42. Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, Oberheim N, Lou N, Wang X, Zielke HR, Kang J, Nedergaard M. An astrocytic basis of epilepsy. *Nat Med* 2005;11:973–981.
43. Porter RJ, Cereghino JJ, Gladding GD, Hessie BJ, Kupferberg HJ, Scoville B, White BG. Antiepileptic drug development program. *Cleve Clin Q* 1984;51:293–305.
44. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.
45. Bohl MA, Turner JD, Little AS, Nakaji P, Ponce FA. Assessing the relevancy of "citation classics" in neurosurgery. Part II: Foundational papers in neurosurgery. *World Neurosurg* 2017;104:939–966.
46. Bohl MA, Ponce FA. Assessing the relevancy of highly cited works in neurosurgery. Part I: The 100 most relevant papers in neurosurgical journals. *World Neurosurg* 2017:104:927–938.
47. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51:676–685.
48. Park KM, Kim SE, Lee BI, Kim HC, Yoon DY, Song, HK, Bae JS. Top 100 cited articles on epilepsy and status epilepticus: A bibliometric analysis. *J Clin Neurosci Off J Neurosurg Soc Australas* 2017;42:12–18.
49. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 1995;15:7539–7547.
50. Sarli CC, Dubinsky EK, Holmes KL. Beyond citation analysis: A model for assessment of research impact. *J Med Libr Assoc* 2010;98:17–23.