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ORIGINAL ARTICLE

The 100 most-cited articles in Parkinson's disease

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Abstract

Background Parkinson's disease (PD), the second most common neurodegenerative disease, has serious clinical effects. Research on PD is increasing, but the quantity and quality of this research have not been reported.

Methods To analyze the most-cited articles on PD and provide information about developments in this field, we searched for articles in the Web of Science for the keyword "Parkinson*" in the title. We selected the 100 most-cited articles and evaluated information including citation number, publication time, journal, impact factor, authors, original country, institution of corresponding author, and study type.

Results Citation numbers for the 100 most-cited articles ranged from 669 to 6902, with a median of 944. The 100 articles were published from 1967 to 2009, with most appearing between 1996 and 2000 ($n = 24$) and 2001 to 2005 ($n = 27$). The publications appeared in a total of 31 journals, led by *Science* with 15 and the *New England Journal of Medicine* (*NEJM*) with 13. The majority (84%) of the 100 most-cited articles had ≥ 3 authors. The articles originated from 14 countries, led by the USA ($n = 44$) and England ($n = 17$). Among the 100 most-cited articles, 24 were clinical studies, 54 were laboratory studies, 20 were reviews, and 2 were clinical guidelines. None of these articles originated from South America, Oceania, or Africa.

Conclusions The present study provides historical perspectives on the progress of PD research and highlights trends and academic achievements in this field.

Keywords Most-cited · Parkinson's disease · Neurodegenerative diseases

Introduction

Parkinson's disease (PD) is the second-most prevalent neurodegenerative disease which characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta [1, 2]. It is a major contributor to worsened medical outcomes, poor quality of life, disability, and nursing home placement [3, 4]. Medical researchers have increasingly explored the mechanisms, early recognition, and prevention of PD. However, the PD research literature has not been analyzed to assess the quality of scientific insights in this area.

Citation analysis is an important method for determining the influence of an article on scientific progress as well as evaluating the impact factor (IF) of a scientific journal [5]. The study of citation analysis may help to identify articles, research topics, and authors of influence.[6]. Attempts have been made to identify the most cited articles in many fields, including neurosurgery,[7], traumatic brain injury [8], orthopedics [9], radiology [10], and surgery [11]. However, no citation analysis of PD has been published. Therefore, we analyzed and characterized the 100 most-cited articles on PD, to obtain an indication of the most impactful advances, developments, and discoveries in this field during the past century.

Jin-hua Xue, Zhi-ping Hu and Ping Lai contributed equally to this work.

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Methods

In September 2017, we performed a citation search on the bibliometric database ISI Web of Science (Philadelphia, PA, USA) from 1900 to 2017 for articles pertaining to PD. The search used the key term "Parkinson*" in the title (*as a wild card character used in search string). Articles on the list were reviewed by two independent reviewers by reading the abstracts. The full texts were acquired from PubMed, EMBASE, or ScienceDirect when necessary. Only studies focused on PD as the main topic and published in English were included. Articles were excluded if they were not pertinent.

We identified and selected the 100 most-cited articles related to PD, which were then manually reviewed by two independent investigators using the modified approach of the methods by Azer [12] and Lim et al. [13]. We compiled the information on the journal name, citation number, IF, title, number of authors, authorship (first, second, and corresponding authors), publication year, and country of origin of each article. If the authors were from multiple countries, the country of origin was deemed to be that of the corresponding author.

Statistical analysis

Data were described by the median or interquartile range. The Wilcoxon rank sum test and Spearman test were used to evaluate different indicators. All data were analyzed with SPSS V.17 software (SPSS, Chicago, IL, USA). All probability values were two-tailed, and statistical significance was defined as $p < 0.05$.

Results

Citation count and publication year

A total of 75,913 articles on PD were identified in the Web of Science core database after the initial search in the period from 1900 to present. We selected the 100 most frequently cited articles and ranked them according to the number of citations listed in Table 1. Citation numbers ranged from 669 to 6902, with a median number of 944. Among them, one article was cited more than 5000 times and 44 articles were cited more than 1000 times. The citation index (median 58, range 22–250) was correlated with number of the citations per article ($r = 0.690$, $p = 0.000$).

The 100 most-cited articles were published between 1967 and 2010, and 51% of these papers were published between 1996 and 2005. Three articles were published before 1970 and none of the articles was produced after 2010. The most productive period was 2001 to 2005, during which 27 articles were published. However, when calculating the mean citation number for each article, those published in 1966 to 1970 had the largest citation number ($n = 3023$) (Fig. 1). The single year with the most cited articles was 2003 ($n = 10$). The number of citations was highest for the period 2001 to 2005 (31,937). The Spearman test indicated an uptrend between the citation index and time ($r = 0.649$, $p < 0.001$). There is low correlation between time and number of citations ($r = -0.299$, $p = 0.03$), but there was a positive correlation between time and citation index ($r = 0.375$, $p < 0.001$).

Journals publishing the top 100 articles

The 100 most-cited articles on PD were published in 31 different journals. All the journals with more than one article are listed in Supplemental Material 1; these were predominantly comprehensive medical publications, led by the *Science* with 15 articles, followed by the *New England Journal of Medicine* (*NEJM*) with 13. In addition, *Nature*, *Proceedings of the National Academy of Sciences of the United States of America*, and the *Annals of Neurology* contributed seven, seven, and six of the most cited articles, respectively. The IFs of the 100 most-cited articles ranged from 4.083 to 72.406. Half of the top 100 articles (50 articles) were published in the high-IF journals (IF > 20). The journal IF was significantly correlated with the number of top 100 articles ($r = 0.645$, $p = 0.005$) and a low correlation with the number of citations ($r = 0.455$, $p = 0.067$).

Authorship, origins and institutions

A majority (84%) of the top 100 articles were produced by 3 or more authors. A list of the most frequently appearing authors is presented in Supplemental Material 2. With regard to individual contributions, A.J. Lees was the most frequently cited author, with listings on 8 of the top 100 articles (as first author, 1; as corresponding author, 3) and a total of 12,132 citations. Dr. Lees was followed by P. Jenner and A.E. Lang, both of whom authored 6 of the top 100 articles, with 5425 and 5340 citations, respectively (Supplemental Material 2). A total of 14 countries contributed to the top 100 articles. As expected, the USA was the most productive country with 44 publications, followed by England (17), France (9), Germany (7), and Canada (5 articles), with all other countries contributing less than 5 publications, as shown in Fig. 2. Articles originating from the USA also had the highest number of citations (total = 57,234). Of the top 100 articles, 8 institutions provided three or more articles. Among them, the leading institutions were University of London with 13 articles, followed by the U.S. National Institutes of Health (NIH) with 6 articles and Harvard University with 5 articles (Supplemental Material 3).

Table 1 The top 100 cited articles on Parkinson's disease

Rank	Author (first)	Title	Journals	Years	Times cited	Citation index	PMID
1	Hoehn, MM	Parkinsonism-onset progression and mortality	*Neurology*	1967	6902	138.04	6,067,254
2	Hughes, AJ	Accuracy of clinical-diagnosis of idiopathic Parkinson's disease—a clinicopathological study of 100 cases	*Journal of Neurology Neurosurgery and Psychiatry*	1992	4873	194.92	1,564,476
3	Polymeropoulos, MH	Mutation in the alpha-synuclein gene identified in families with Parkinson's disease	*Science*	1997	4483	224.15	9,197,268
4	Braak, H	Staging of brain pathology related to sporadic Parkinson's disease	*Neurobiology of Aging*	2003	3510	250.71	12,498,954
5	Langston, JW	Chronic parkinsonism in humans due to a product of meperidine-analog synthesis	*Science*	1983	3283	96.56	6,823,561
6	Kitada, T	Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism	*Nature*	1998	2870	151.05	9,560,156
7	Kruger, R	Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease	*Nature Genetics*	1998	2455	129.21	9,462,735
8	Dauer, W	Parkinson's disease: mechanisms and models	*Neuron*	2003	2266	161.86	12,971,891
9	Singleton, AB	Alpha-synuclein locus triplication causes Parkinson's disease	*Science*	2003	2234	159.57	14,593,171
10	Betarbet, R	Chronic systemic pesticide exposure reproduces features of Parkinson's disease	*Nature Neuroscience*	2000	2012	118.35	11,100,151
11	Burns, RS	A primate model of parkinsonism-selective destruction of dopaminergic-neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	*Proceedings of The National Academy of Sciences of The United States of America-Biological Sciences*	1983	1985	58.38	6,192,438
12	Gibb, WRG	The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease	*Journal of Neurology Neurosurgery and Psychiatry*	1988	1925	66.38	2,841,426
13	Bernheimer, H	Brain dopamine and syndromes of Parkinson and Huntington clinical, morphological and neurochemical correlations	*Journal of The Neurological Sciences*	1973	1890	42.95	4,272,516
14	Fearnley, JM	Aging and Parkinson's disease substantia nigra regional selectivity	*Brain*	1991	1656	63.69	1,933,245
15	Valente, EM	Hereditary early-onset Parkinson's disease caused by mutations in PINK1	*Science*	2004	1591	122.38	15,087,508
16	Gelb, DJ	Diagnostic criteria for Parkinson disease	*Archives of Neurology*	1999	1495	83.06	9,923,759
17	Spillantini, MG	Alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies	*Proceedings of The National Academy of Sciences of The United States of America*	1998	1469	77.32	9,600,990
18	Mcgeer, PL	Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains	*Neurology*	1988	1458	50.28	3,399,080
19	Bonifati, V	Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism	*Science*	2003	1431	102.21	12,446,870
20	Zarranz, JJ	The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia	*Annals of Neurology*	2004	1428	109.85	14,755,719
21	Zimprich, A	Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology	*Neuron*	2004	1409	108.38	15,541,309
22	Freed, CR	Transplantation of embryonic dopamine neurons for severe Parkinson's disease	*New England Journal of Medicine*	2001	1407	87.94	11,236,774
23	Shimura, H	Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase	*Nature Genetics*	2000	1307	76.88	10,888,878
24	Kish, SJ	Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease-pathophysiologic and clinical implications	*New England Journal of Medicine*	1988	1270	43.79	3,352,672
25	Feany, MB	A Drosophila model of Parkinson's disease	*Nature*	2000	1256	73.88	10,746,727
26	Paisan-Ruiz, C	Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease	*Neuron*	2004	1248	96	15,541,308
27	Lang, AE	Parkinson's disease—first of two parts	*New England Journal of Medicine*	1998	1248	65.68	9,761,807
28	Schapira, AHV	Mitochondrial complex I deficiency in Parkinson's disease	*Journal of Neurochemistry*	1990	1244	46.07	2,154,550
29	Bergman, H	Reversal of experimental parkinsonism by lesions of the subthalamic nucleus	*Science*	1990	1237	45.81	2,402,638
30	Jankovic, J	Parkinson's disease: clinical features and diagnosis	*Journal of Neurology Neurosurgery and Psychiatry*	2008	1210	134.44	18,344,392
31	Krack, P	Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease	*New England Journal of Medicine*	2003	1151	82.21	14,614,167
32	Limousin, P	Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease	*New England Journal of Medicine*	1998	1137	59.84	9,770,557
33	de Lau, LML	Epidemiology of Parkinson's disease	*Lancet Neurology*	2006	1125	102.27	16,713,924
34	Cotzias, GC	Aromatic amino acids and modification of parkinsonism	*New England Journal of Medicine*	1967	1106	22.12	5,334,614
35	Javitch, JA	Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity	*Proceedings of The National Academy of Sciences of The United States of America*	1985	1102	34.44	3,872,460
36	Leroy, E	The ubiquitin pathway in Parkinson's disease	*Nature*	1998	1087	57.21	9,774,100
37	Cotzias, GC	Modification of parkinsonism-chronic treatment with L-dopa	*New England Journal of Medicine*	1969	1060	22.08	4,178,641
38	Dawson, TM	Molecular pathways of neurodegeneration in Parkinson's disease	*Science*	2003	1057	75.5	14,593,166
39	Braak, H	Stages in the development of Parkinson's disease-related pathology	*Cell and Tissue Research*	2004	1056	81.23	15,338,272
40	Kim, JH		*Nature*	2002	1055	70.33	12,077,607

Table 1 (continued)

Rank	Author (first)	Title	Journals	Years	Times cited	Citation index	PMID
		Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease					
41	Davis, GC	Chronic parkinsonism secondary to intravenous-injection of meperidine analogs	*Psychiatry Research*	1979	1047	27.55	298,352
42	Dexter, DT	Basal lipid-peroxidation in substantia nigra is increased in Parkinson's disease	*Journal of Neurochemistry*	1989	1038	37.07	2,911,023
43	Deuschl, G	A randomized trial of deep-brain stimulation for Parkinson's disease	*New England Journal of Medicine*	2006	1032	93.82	16,943,402
44	Riederer, P	Transition-metals, ferritin, glutathione, and ascorbic-acid in parkinsonian brains	*Journal of Neurochemistry*	1989	1023	36.54	2,911,028
45	Conway, KA	Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy	*Proceedings of The National Academy of Sciences of The United States of America*	2000	991	58.29	10,639,120
46	Tomlinson, CL	Systematic review of levodopa dose equivalency reporting in Parkinson's disease	*Movement Disorders*	2010	983	140.43	21,069,833
47	Chartier-Harlin, MC	Alpha-synuclein locus duplication as a cause of familial Parkinson's disease	*Lancet*	2004	964	74.15	15,451,224
48	Rascol, O	A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa	*New England Journal of Medicine*	2000	964	56.71	10,816,186
49	Baba, M	Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies	*American Journal of Pathology*	1998	961	50.58	9,546,347
50	Emre, M	Clinical diagnostic criteria for dementia associated with Parkinson's disease	*Movement Disorders*	2007	959	95.9	17,542,011
51	Conway, KA	Accelerated in vitro fibril formation by a mutant alpha-synuclein linked to early-onset Parkinson disease	*Nature Medicine*	1998	929	48.89	9,809,558
52	Carlsson, M	Interactions between glutamatergic and monoaminergic systems within the basal ganglia—implications for schizophrenia and Parkinson's disease	*Trends in Neurosciences*	1990	923	34.19	1,695,402
53	Forno, LS	Neuropathology of Parkinson's disease	*Journal of Neuropathology and Experimental Neurology*	1996	921	43.86	8,786,384
54	Chaudhuri, KR	Non-motor symptoms of Parkinson's disease: diagnosis and management	*Lancet Neurology*	2006	912	82.91	16,488,379
55	Olanow, CW	Etiology and pathogenesis of Parkinson's disease	*Annual Review of Neuroscience*	1999	902	50.11	10,202,534
56	Limousin, P	Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation	*Lancet*	1995	889	40.41	7,815,888
57	Goetz, CG	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results	*Movement Disorders*	2008	870	96.67	19,025,984
58	Lucking, CB	Association between early-onset Parkinson's disease and mutations in the parkin gene	*New England Journal of Medicine*	2000	868	51.06	10,824,074
59	Simon-Sanchez, J	Genome-wide association study reveals genetic risk underlying Parkinson's disease	*Nature Genetics*	2009	866	108.25	19,915,575
60	Jenner, P	Oxidative stress in Parkinson's disease	*Annals of Neurology*	2003	864	61.71	12,666,096
61	Bergman, H	The primate subthalamic nucleus. 2. Neuronal-activity in the MPTP model of parkinsonism	*Journal of Neurophysiology*	1994	859	37.35	7,983,515
62	Kordower, JH	Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease	*Science*	2000	856	50.35	11,052,933
63	Lees, AJ	Parkinson's disease	*Lancet*	2009	844	105.5	19,524,782
64	Schapira, AHV	Mitochondrial complex I deficiency in Parkinson's disease	*Lancet*	1989	840	30	2,566,813
65	Frank, MJ	By carrot or by stick: cognitive reinforcement learning in Parkinsonism	*Science*	2004	837	64.38	15,528,409
66	Fahn, S	Levodopa and the progression of Parkinson's disease	*New England Journal of Medicine*	2004	823	63.31	15,590,952
67	Obeso, JA	Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease	*New England Journal of Medicine*	2001	823	51.44	11,575,287
68	Hirsch, E	Melanized dopaminergic-neurons are differentially susceptible to degeneration in Parkinson's disease	*Nature*	1988	823	28.38	2,899,295
69	Olanow, CW	A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease	*Annals of Neurology*	2003	818	58.43	12,953,276
70	Wu, DC	Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease	*Journal of Neuroscience*	2002	812	54.13	11,880,505
71	Laitinen, LV	Leksells posteroventral pallidotomy in the treatment of Parkinson's disease	*Journal of Neurosurgery*	1992	806	32.24	1,727,169
72	Lindvall, O	Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease	*Science*	1990	805	29.81	2,105,529
73	Parker, WD	Abnormalities of the electron-transport chain in idiopathic Parkinson's disease	*Annals of Neurology*	1989	800	28.57	2,557,792
74	Auluck, PK	Chaperone suppression of alpha-synuclein toxicity in a Drosophila model for Parkinson's disease	*Science*	2002	787	52.47	11,823,645
75	Bjorklund, LM	Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model	*Proceedings of The National Academy of Sciences of The United States of America*	2002	781	52.07	11,782,534
76	Gill, SS	Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease	*Nature Medicine*	2003	778	55.57	12,669,033
77	Cummings, JL	Depression and Parkinson's disease—a review	*American Journal of Psychiatry*	1992	756	30.24	1,372,794

Table 1 (continued)

Rank	Author (first)	Title	Journals	Years	Times cited	Citation index	PMID
78	Shimura, H	Ubiquitination of a new form of alpha-synuclein by parkin from human brain: Implications for Parkinson's disease	*Science*	2001	753	47.06	11,431,533
79	Dexter, DT	Increased nigral iron content and alterations in other metal-ions occurring in brain in Parkinson's disease	*Journal of Neurochemistry*	1989	747	26.68	2,723,638
80	Liberatore, GT	Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease	*Nature Medicine*	1999	733	40.72	10,581,083
81	Markey, SP	Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism	*Nature*	1984	731	22.15	6,332,988
82	Wernig, M	Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease	*Proceedings of The National Academy of Sciences of The United States of America*	2008	725	80.56	18,391,196
83	Hughes, AJ	What features improve the accuracy of clinical-diagnosis in Parkinson's disease—a clinicopathological study	*Neurology*	1992	723	28.92	1,603,339
84	Taylor, AE	Frontal-lobe dysfunction in Parkinson's disease—the cortical focus of neostriatal outflow	*Brain*	1986	718	23.16	3,779,372
85	Lang, AE	Parkinson's disease—second of two parts	*New England Journal of Medicine*	1998	717	37.74	9,770,561
86	Fahn, S	The oxidant stress hypothesis in Parkinson's disease-evidence supporting it	*Annals of Neurology*	1992	716	28.64	1,471,873
87	Gash, DM	Functional recovery in parkinsonian monkeys treated with GDNF	*Nature*	1996	709	33.76	8,637,574
88	Moore, DJ	Molecular pathophysiology of Parkinson's disease	*Annual Review of Neuroscience*	2005	697	58.08	16,022,590
89	Sian, J	Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia	*Annals of Neurology*	1994	692	30.09	8,080,242
90	Jahanshahi, M	Self-initiated versus externally triggered movements. 1. An investigation using measurement of regional cerebral blood-flow with PET and movement-related potentials in normal and Parkinson's disease subjects	*Brain*	1995	690	31.36	7,655,888
91	Cooper, AA	alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models	*Science*	2006	688	62.55	16,794,039
92	Aarsland, D	Prevalence and characteristics of dementia in Parkinson disease—an 8-year prospective study	*Archives of Neurology*	2003	688	49.14	12,633,150
93	Yoritaka, A	Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease	*Proceedings of The National Academy of Sciences of The United States of America*	1996	688	32.76	8,610,103
94	Anglade, P	Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease	*Histology and Histopathology*	1997	685	34.25	9,046,040
95	Gradinaru, V	Optical deconstruction of parkinsonian neural circuitry	*Science*	2009	681	85.13	19,299,587
96	Hirsch, EC	Neuroinflammation in Parkinson's disease: a target for neuroprotection?	*Lancet Neurology*	2009	676	84.5	19,296,921
97	Bender, A	High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease	*Nature Genetics*	2006	675	61.36	16,604,074
98	Li, JY	Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation	*Nature Medicine*	2008	672	74.67	18,391,963
99	Spencer, PS	Guam amyotrophic-lateral-sclerosis parkinsonism dementia linked to a plant excitant neurotoxin	*Science*	1987	670	22.33	3,603,037
100	Blum, D	Molecular pathways involved in the neurotoxicity of 6-OHDA, dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease	*Progress in Neurobiology*	2001	669	41.81	11,403,877

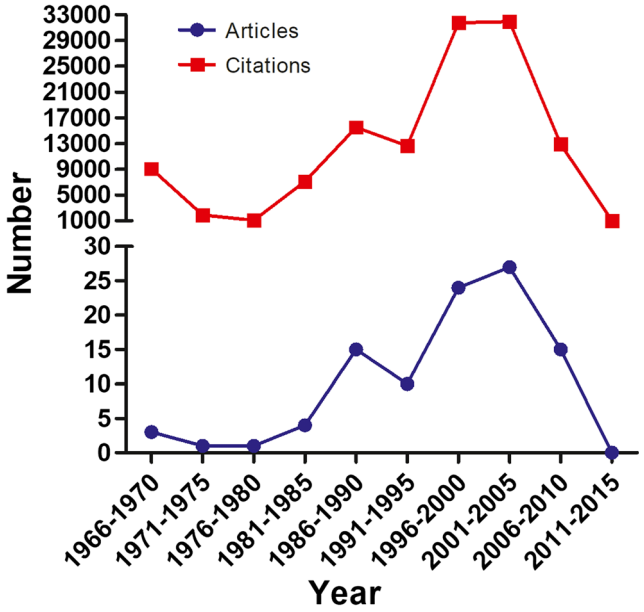

Fig. 1 Numbers and number of citations of top 100 cited articles in 5-year periods

Publication type

Among the 100 most-cited articles, there were 24 clinical studies, 54 laboratory studies, 20 reviews, and 2 clinical guidelines (Fig. 3). The number of total citations per article ranged from 688 to 6902 (median, 869) for clinical studies and from 670 to 4873 (median, 1007) for laboratory studies. Of the 24 clinical articles, surgical therapies were addressed by 10 articles, medical therapies by 5, clinical function by 4, clinical genetics by 2, case reports by 2 articles, and clinical staging by 1 article. In particular, the surgical studies focused on deep brain stimulation (five studies), cellular transplantation (three studies), pallidotomy (one study), and intraputaminal delivery of glial cell-derived neurotrophic factor (GDNF) (one study). All the reports of medical therapy were published in high-IF journals, four in the *NEJM* and one in *Science*. We found that 8 of the 10 surgical research papers were published in high-IF journals: 5 in the *NEJM* and 1 each in the *Lancet*, *Science*, and *Nature Medicine*. The earliest study included in the top 100 cited articles on medical therapy was published in 1967, while the earliest study on surgical therapy was published in 1990. Furthermore, the studies of medical therapy had higher median citations per article than the surgical studies (median 964 vs. 856). In the laboratory studies, 18 articles used animal models and 15 articles addressed brain pathology, 11 articles focused on identifying genetic mutations, and 10 articles evaluated the cellular and molecular biology of PD. We also found that 52% of the laboratory studies appeared in the *NEJM*, *Lancet*, *Science*, or one of the *Nature* journals (*Nature, Nature Genetics, Nature Medicine*, and *Nature Neuroscience*). Among them, the articles about brain pathology were most frequently cited ($n = 22{,}475$), followed by articles addressing genetic mutations ($n = 21{,}200$).

Discussion

PD is the second most common neurodegenerative disease, affecting approximately 1% of the population over the age of 60 and 4% over 80 [14]. The current study is the first to assess the characteristics of the 100 most-cited articles in the field of PD, and it allowed us to recognize historical patterns and trends in PD research, which has undergone considerable change in recent years. The results may facilitate recognition of important advances and prevalent areas of research interest in PD and may help basic scientists and clinicians design future research. The current study helps to identify classical research and high-impact journals by providing information regarding authors, institutions, and journals.

Citation analysis is a useful bibliometric method, introduced in 1987, that has been widely used in various fields and has proven to be important for both authors and journals. For authors, citation analysis not only helps them to recognize important research progress but also helps add useful perspectives on historical developments in areas of academic interest. For journals, data from citation analyses may attract manuscripts with higher citation potentials. In addition, citation analysis may, to some extent, help researchers produce better work. However, we must recognize that since the citation number for any given paper is strongly influenced by the prominence of the journal of publication, it may not have a great relationship with the scientific merit of the manuscript [15, 16], and at the same time, the citation number could also be affected by factors such as the author's geographical origin,

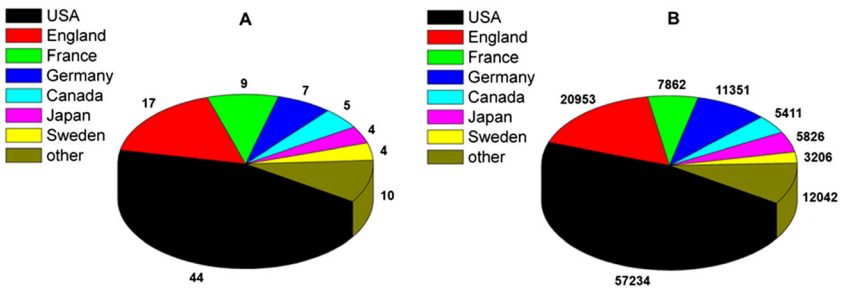

Fig. 2 The top 100 articles were analyzed in terms of their country of origin. **a** Number of articles from each country. **b** Number of citations for the articles from each country

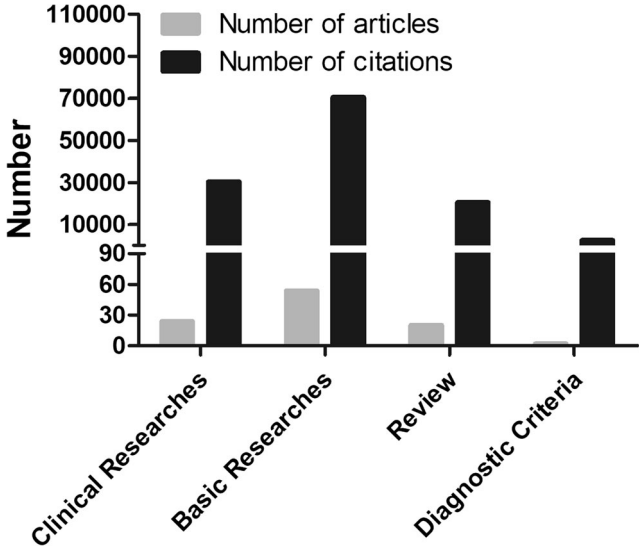

Fig. 3 Distributions of research type of the top 100 cited articles on Parkinson's disease

language, and gender [17, 18]. Although there are some disadvantages with evaluating the quality of the article by its citation rating, it is still the most widely accepted current method to determine the merits of a paper or journal [19]. At present, more and more articles are labeled as "top cited" or "the most cited" in various medical disciplines, but there is a paucity of literature on citations of articles about PD.

PD, the incidence of which gradually increases with age, is a major global health problem that is associated with increased medical costs and thus places a heavy burden on some communities. In recent years, there have been significant changes in strategies for the prevention, diagnosis, and treatment of PD. Therefore, there is an urgent need to find appropriate directions for research as well as to better design future studies. This may be accomplished through analyzing classic articles to better understand the history and development of PD research. The current study is the first to assess the leading article citations in PD research and will contribute to the ability of authors or readers to recognize the quality of the research reports, identify the key discoveries that have been made as a result of past efforts, and illuminate developing trends in scientific research.

It is well established that the number of citations an article garners is affected by the date of publication [20]. The longer the time since the article was published, the greater the chance of being cited. However, unlike the majority of citation analyses which report peaks between 1980 and 1995, in this analysis, the most productive period was 1996 to 2005, which may be partially accounted for by an increase in numbers of articles and improvements in research quality. In order to overcome the impact of the publication time on the likelihood of citation, we also assessed the citation index as a measure of the true impact of an article independent of short-term trends. The results were consistent with an increase of articles and improvements in research quality.

High-IF journals attract submissions from authors because they not only potentially provide prominence for the research results but also help the author get more attention. The IF of a journal is the most important predicator for citations, and most top-cited articles are published in high-IF journals [21, 22]. This study also confirmed that the IF was positively related to the top 100 cited articles and the number of citations. When taking into account the 5-year IF of the journals, 52 articles were published in the high-IF journals (IF > 20), 23 articles were published in journals with IF between 10 and 20, and only 12 articles were published in the low-IF journals (IF < 5). In the clinical realm, most articles on medical and surgical therapies were published in the highest impact general medical journal (the *NEJM*). And most animal and basic laboratory studies were published in the high-IF science journals *Nature* and *Science*. These results further validate the hypothesis that researchers tend to cite papers from a few core journals in their specialty [23]. In addition, the *Proceedings of the National Academy of Sciences of the United States of America* and the *Annals of Neurology* were the sources for several articles in this study.

Fourteen countries contributed to the 100 most-cited articles. The USA ranked first, similar to the citation analyses in other specialties [24–26]. This finding confirms the important influence of the USA in the study of PD worldwide, which can be explained by the large scientific community and enormous financial resources available to it. Among the top 16 institutions, 11 (69%) are in the USA. Moreover, although authors usually prefer to publish in their local journals, authors in American and European countries tended to publish in American journals [27]. However, the leading institution for publications in PD is the University College of London, which published 13 of the 100 most-cited articles with 17,048 total citations. The most frequently cited authors, A.J. Lees and P. Jenner, were both from the University College of London and had 8 and 6 articles that were on the list, respectively, that reported results of laboratory studies. In addition, we found that no authors from Africa, Oceania, or South America contributed to the 100 most-cited works, which may be related to information access, difficulties in research, and language barriers in these areas, indicating a great disparity in scientific publications between the developing and developed regions of the world.

PD was first described in 1817, and although significant efforts have been made during the past several decades, the pathogenesis of PD remains unclear. Therefore, the study of the pathogenesis of PD is still an area of active interest, which is consistent with our findings that most of the top 100 cited articles (54%) in the present

study report the results of basic research. The median citation number per basic research article was higher than that of clinical research articles (1007 vs. 869). Among laboratory studies, the most frequent types were descriptive animal models ($n = 18$), followed by neuropathological studies ($n = 15$), characterizing genetics ($n = 11$), and evaluations of cellular and molecular biology ($n = 10$).

Research directions constantly change with time. In the 1970s, research was mainly focused on motor fluctuations from L-dopa therapy, assessment of secondary PD, and attempts to further characterize PD. In the 1980s, in addition to the side effects of levodopa treatment, studies addressed cognitive dysfunction, surgical transplantation of stem cells, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models, and the role of oxidative degeneration in the pathogenesis of PD. In the 1990s, attention focused on surgical treatments such as pallidotomy, deep brain stimulation, and stem cell transplantation, as well as the role of gene mutations and synuclein in the pathogenesis of disease. After 2000, the studies tended to focus on the efficacy of deep brain stimulation (DBS), the therapeutic effects of stem cells and neurotrophic factors, and other gene mutations such as leucine-rich repeat kinase 2 (LRRK2), DJ-1 (protein deglycase, also known as Parkinson disease protein 7), and PTEN-induced putative kinase 1 (PINK1) that can also lead to PD.

Limitations

Although we attempted to rule out all possible design flaws, there are still some limitations in the current study. First, we applied a direct and reproducible approach that clearly limits the references to those with "Parkinson's disease" in the title of the article, which may lead to omission of some publications related to the disease. For instance, papers that referenced "Parkinson's disease" in the abstract or keywords, but not in the title, were omitted from our study. Second, despite a meticulous search of the Web of Science, citation information can also be obtained from Google Scholar and Scopus, which may show different results [28, 29] and lead to some research reports being missed. Third, this kind of study of IFs favors earlier published articles, often excluding newly published high-quality studies that have not had the opportunity yet to gain sufficient citations. Fourth, the number of citations alone cannot fully quantify the value of the contribution to the field and may miss important, influential but less frequently cited papers. Fifth, the effect of self-citation and citations of irrelevant articles can also increase the overall citation rate, and this possibility was not addressed in the design of our study. Finally, the language of publication was restricted to English, which would also generate bias.

Conclusions

The current citation analysis dealt with most of the influential studies on PD and presented a detailed list that will change dynamically as the field moves forward. Our analysis has collected a number of highly influential articles from a variety of perspectives, including medical and surgical treatment, basic research, clinical research, and characterization and classification of the disease using pathological methods, and highlights the research trends and academic achievements. Our analysis also provides an insight into the frequency of citations on PD and reveals the quality of research, discoveries, and trends steering PD research worldwide.

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Compliance with ethical standards

Conflict of interest None declared.

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