Bibliometric Analysis of Exercise and Neuropathic Pain Research

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Background: Neuropathic pain, a type of chronic pain, is difficult to treat clinically. Mounting evidence suggests that exercise can effectively ease neuropathic pain, and the number of publications related to exercise and neuropathic pain has increased over time. However, bibliometrics is rarely used in analyzing the general aspects of studies on exercise and neuropathic pain. The present study aims to provide a systematic overview of global scientific research related to exercise and neuropathic pain from 2005 to 2019.

Methods: Publications on Science Citation Index – Expanded of Web of Science from 2005 to 2019 were searched, and those related to exercise and neuropathic pain were analyzed. Only English papers were included without specific species restrictions.

Results: A total of 676 papers were included in accordance with our adopted criteria. Linear regression analysis showed a statistically meaningful increase in the number of publications on exercise and neuropathic pain study over time ($p < 0.001$). The subject categories of the 676 papers mainly focused on neuroscience (29.88%), clinical neurology (18.79%) and rehabilitation (10.06%) in Web of Science. In terms of contribution to scientific research on exercise and neuropathic pain, the United States led the first echelon and had the largest numbers of published papers, citations and H-index.

Conclusion: The findings in our study may provide researchers useful information about research trends and frontiers, cooperators and cooperative institutions.

Keywords: exercise, neuropathic pain, bibliometrics, research trends

Introduction

In 2011, neuropathic pain was defined as “pain directly caused by a lesion or disease affecting the somatosensory system either at peripheral or central level”.¹ The common reasons for neuropathic pain include diabetic peripheral neuropathy,² spinal cord injury,³ cancer^{4,5} and sciatic nerve injury.⁶

Neuropathic pain, a type of chronic pain, can affect physical and psychological functions, reduce work efficiency and lead to disability in severe cases.^{7,8} In a French population, the prevalence of chronic pain is 31.7%. Among the patients with chronic pain, 21.7% have neuropathic characteristics.⁹ The prevalence of chronic pain with neuropathic characteristics is 0.9%–17.9%.¹⁰ Furthermore, neuropathic pain has a higher intensity and duration than chronic pain without neuropathic features.¹¹ These data show that the prevalence of neuropathic pain is not low and neuropathic pain is worth studying.

The clinical management of neuropathic pain is complex, and pharmacologic and nonpharmacologic measures are used in alleviating this type of pain. However, pharmacologic measures are unsatisfactory, that is, only 40%–60% of patients who undergo

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these measures experience relief from neuropathic pain.¹² The long-term use of drugs may cause adverse effects.¹³ Exercise is one of the therapies recommended by clinical practice guidelines for neuropathic pain.¹⁴ The effect of exercise on neuropathic pain has been demonstrated in rats,¹⁵ but the underlying mechanisms remain unclear. The use of exercise therapy in reducing neuropathic pain in patients is relatively new.¹⁶ Studying exercise for neuropathic pain is significant, which can help patients get rid of the adverse effects of drugs, relief from pain and improve life quality.

In recent years, studies on exercise and neuropathic pain have increased, but few clinical studies analyzed the general aspects of exercise and neuropathic pain. Bibliometric analysis has been used in several pain-related areas, such as low back pain^{17–19} and pediatric pain.²⁰ The present study aims to provide systematic information about global exercise and neuropathic pain studies from 2005 to 2019 and quantitative information about the distribution of countries, institutions, journals and authors. CiteSpace V (Drexel University, Philadelphia, United States) was used in bibliometric analysis. The bibliometric analysis of global exercise and neuropathic pain scientific research included the number of publications, contribution and cooperation of authors/countries/institutions, co-citation analysis of references/authors and keyword analysis with the strongest citation bursts. It has significant benefits in terms of providing researchers with the status and trends of research on exercise and neuropathic pain.

Methods

Sources of Data

Publications from the past 15 years (from 2005 to 2019) were searched and downloaded from the Science Citation Index Expanded (SCI-Expanded) of Web of Science. Our retrieval strategy was as follows: TI= (exercise OR locomotion OR run* OR swim* OR “environmental enrichment” OR treadmill OR aerobic\$ OR strength\$ OR isometric\$ OR isotonic\$ OR isokinetic\$ OR endurance OR weight\$ OR resistance OR train*) AND TS= (Neuralgia\$ OR Neurodynia\$ OR “Neuropathic pain” OR sciatica OR “nerve crush” OR “Nerve pain\$” OR “nerve cut” OR “nerve constriction” OR “nerve inflammation” OR “nerve injury” OR “nerve ligation” OR “peripheral neuropathy” OR “chronic constriction injury” OR “diabetic neuropathy”).

Inclusion Criteria

Publications on exercise and neuropathic research in different academic journals, such as *Pain*, *PLoS One* and

Muscle Nerve, were included. Only English papers were included; document types and specific species were not restricted. The document types mainly contained article, meeting abstract and review.

Data Extraction

EndNote X7 (Bld 7072, Thomson Research Soft, Stamford, CA, USA) and Microsoft Office Excel were used in extracting the publications we downloaded. Related data, such as the amount of publications, citations, H-index, journal, reference and keyword, were extracted and recorded as bibliometric indicators.

The amount of publications, citations (including self-citations), citations per paper (the citations of a collection divided by the amount of publications in the collection), H-index and open access were extracted from Web of Science. In the search results from Web of Science, we refined some collections, such as a certain year, a certain country and a certain institution. After that, we created citation reports and gained the data. The amount of publications refers to the quantitative contribution of papers of a collection. The citations are the total number of cited times to all items in a collection that can generally reflect the quality of publications. The H-index was measured on the basis of the quantity of papers and citation frequency for academic journals or researchers. For instance, the H-index of an academic journal or a researcher is H, which means that the journal or researcher has published H papers with at least H citation frequency. Open access refers to the amount of publications that the peer-reviewed versions of the publications can freely access from either the website of publishers or repository.

Statistical Analysis

CiteSpace V and Microsoft Excel were used in (1) obtaining the global output and growth trend of publications, (2) assessing the distribution of journals, authors, countries/regions and institutions, (3) analyzing collaborations between authors, countries/regions and institutions, (4) counting citations and H-index, and (5) analyzing references and keywords. The annual percentage of each subject category of Web of Science (the quantity of annually published papers divided by the total number of published papers for each category) was calculated. IBM SPSS Statistics 21.0 (SPSS, Inc., Chicago, IL, USA) was used in calculating changes in percentage and determining whether the changes are statistically significant. Linear regression analyses were conducted, and each respective

category was used as a dependent variable, and year was used as an independent variable. A p -value of <0.05 was considered significant.

Results

Output and Growth Trends of Publications

Seven non-English papers were removed, and 676 papers that met our criteria were selected ([Supplementary Figure 1](#)). The trend of annually published papers increased from 20 in 2005 to 79 in 2019 ([Figure 1A](#)). Linear regression analysis showed a statistically significant increase in the percentage of publications in 15 years ($t = 11.709$, $p < 0.001$). The 676 papers were cited 9398 times (citations per paper 13.9, H-index 46). As shown in [Figure 1B](#), the number of citations per year increased from 3 in 2005 to 1644 in 2019, and the increase was statistically significant ($t = 13.640$, $p < 0.001$). The citations per

year refer to the total number of citations in one year of all published papers.

Among the five 3-year periods (2005–2007, 2008–2010, 2011–2013, 2014–2016 and 2017–2019), the largest average number of citations per item (27.96) was found in 2005–2007, the highest number of citations (2980) and H-index (33) were found in 2011–2013, the largest number of citations in 2019 (606) was found in 2014–2016, the highest number of publications (221) and open access papers (89) were found in 2017–2019 ([Figure 2](#)).

Subject Categories of Web of Science

A total of 82 subject categories contributed to the 676 publications on exercise and neuropathic pain research. The top 20 subject categories in terms of the amount of publications are shown in [Figure 3](#). Among the top 20 subject categories, Neurosciences had the greatest number of published papers

Figure 1 The number of publications and citations. **(A)** The number of annual publications on exercise and neuropathic pain research from 2005 to 2019. **(B)** The number of annual citations on exercise and neuropathic pain research from 2005 to 2019.

Figure 2 Number of papers, citations, citations per paper, open access paper, H-index and citations in 2019 for each 3-year time period.

Figure 3 The number of papers, citations, citations per paper, open access papers and H-index of the top 20 subject categories of Web of Science.

(202), citations (3719) and open access papers (89) and the highest H-index (34). Anesthesiology had the highest average number of citations per item (26.64). Linear regression analysis indicated that the percentage statistically increased ($p < 0.001$) with time in the top 20 subject categories (Neurosciences, Clinical Neurology, Rehabilitation, Endocrinology Metabolism, Sport Sciences, Orthopedics, Oncology, Physiology, Anesthesiology, Pharmacology Pharmacy, Surgery, Medicine General Internal, Medicine Research Experimental, Multidisciplinary Sciences, Biochemistry Molecular Biology, Engineering Biomedical, Cell Biology, Health Care Science Services, Radiology Nuclear Medicine Medical Imaging and Geriatrics Gerontology).

Distribution of Journals

A total of 364 academic journals contributed to exercise and neuropathic pain research ([Supplementary Table 1](#)). The top 10 journals by publication contributed to 18.2% (123 papers) of the total number of publications ([Table 1](#)). Among the top 10 journals, *Pain* (impact factor or IF 2018, 6.029), *PLoS One* (IF 2018, 2.776) and *Muscle Nerve* (IF 2018, 2.393) had considerable contributions to the number of publications (16 publications per journal, 2.37%). *Pain* was the most cited (491 citations) and had the highest impact factor (IF) 2018 (6.029) and H-index (11). *PLoS One* had the greatest

number of open access papers (16). *Journal of Diabetes and its Complications* had the highest average of citations per item (40.56; IF 2018, 2.684). Among the 10 journals, 56.25% were Q1 (Q1 represents the top 25% of IF distribution), 12.5% journals were Q2 (Q2 represents 25–50% of IF distribution), and 31.25% journals were Q3 (Q3 represents 50–75% of IF distribution) according to the journal IF quartile of Web of Science.

[Figure 4](#) shows the dual map of the journals; the left side is the map of citing journals, and the right side is the map of the cited journals. The lines pointing from the citing journals to the cited journals represent the citation connections and the labels derived from the disciplines included in the journals. The horizontal axes of the ellipses represent the number of authors, whereas the vertical axes of the ellipses are the number of publications. The map shows that the most contributed journals were from neurology, sports and ophthalmology fields, and these journals mostly cited journals from molecular, biology and genetics fields.

Distribution of Countries and Institutions

A total of 57 countries/regions contributed to 676 papers on exercise and neuropathic pain research ([Supplementary Table 2](#)). The top 10 countries/regions by the number of publications are shown in [Figure 5](#). The United States had

Table 1 The Top 10 Journals of Origin of Papers on Exercise and Neuropathic Pain Research

Journals	Papers	Citations (WoS)	Citations per Paper	Open Access	WoS Categories	IF (2018)	Quartile	H-index
<i>Muscle Nerve</i>	16	177	11.06	3	Clinical Neurology; Neurosciences	2.393	Q3; Q3	7
<i>Pain</i>	16	491	30.69	8	Anesthesiology; Clinical Neurology; Neurosciences	6.029	Q1; Q1; Q1	11
<i>PLoS One</i>	16	151	9.44	16	Multidisciplinary Sciences	2.776	Q2	7
<i>Journal of Pain</i>	14	211	15.07	4	Clinical Neurology; Neurosciences	5.424	Q1; Q1	7
<i>Medicine and Science in Sports and Exercise</i>	13	49	3.77	2	Sport Sciences	4.478	Q1	3
<i>Journal of Neuroscience</i>	10	398	39.80	10	Neurosciences	4.204	Q1	8
<i>Neuroscience</i>	10	254	25.40	1	Neurosciences	3.244	Q2	6
<i>Physical Therapy</i>	10	272	27.20	10	Orthopedic; Rehabilitation	3.043	Q1; Q1	8
<i>Journal of Diabetes and its Complications</i>	9	365	40.56	3	Endocrinology Metabolism	2.684	Q3	6
<i>Journal of the Peripheral Nervous System</i>	9	38	4.22	0	Clinical Neurology; Neurosciences	2.441	Q3; Q3	4

Abbreviations: WoS, Web of Science; IF, impact factor.

Figure 4 The dual-map overlay of journals related to exercise and neuropathic pain research.

Figure 5 The number of papers, citations, citations per paper, open access papers and H-index of the top 10 countries/regions.

the highest number of publications (252), the most citations (5107), the most citations per paper (20.27), and the most open access papers (137) and the highest H-index (39), followed by Brazil (58 publications) and China (51 publications). Figure 6A shows the widespread collaboration between countries/regions. The overview of all the countries contributing to the 676 papers is presented in a world map according to the number of published papers (Figure 7).

A total of 1003 institutions published papers on exercise and neuropathic pain research (Supplementary Table 3). Figure 8 shows the top 10 institutions by the number of papers. The University of Sao Paulo had the largest number

of publications (23), followed by Emory University (18), which had the highest H-index (12) and number of open access papers (15). Harvard University had the highest number of citations (525) and highest average of citations per item (52.5). Figure 6B shows the collaborations between institutions. However, cooperation was relatively rare.

Distribution of Authors

The 676 papers on exercise and neuropathic pain research were contributed by 3148 authors. Among the top 10 authors by the numbers of published papers (Table 2), English AW contributed 14 papers ranking first, followed by Ilha J and

Figure 6 The analysis of countries/regions and institutions. **(A)** Network map of countries/regions engaged in exercise and neuropathic pain research. **(B)** Network map of institutions engaged in exercise and neuropathic pain research.

Figure 7 World map of total country output based on exercise and neuropathic pain research.

Weight DE (12 publications). Among the top 10 co-cited authors (Table 2), Stagg NJ and Chen YW were co-cited 46 times, followed by Kuphal KE and Balducci S (44 times). The cooperation between authors is shown in Figure 9.

Analysis of References

Analysis of reference is an important part of bibliometrics study. Figure 10 is the timeline view of the co-citation analysis of references, with the top 10 clusters. The clusters were named by the index terms in

Figure 8 The number of papers, citations, citations per paper, open access papers and H-index of the top 10 institutions.

cited references. The modularity Q value reflects the significance of community structure. A Q value higher than 0.3 corresponds to a significant community structure. In the present study, the Q value was 0.8815. The largest cluster #0 was “axon regeneration,” followed by “stress” (#1), “intraepidermal nerve fiber density,” (#2) and “tai chi” (#3).

Analysis of Keywords

CiteSpace V was used to extract the keywords of the 676 publications on exercise and neuropathic pain research. Figure 11 shows that the top 18 keywords with the strongest citation bursts since 2005 were surgery and those since 2006 were recovery. Keywords with the strongest citation bursts by the end of 2019 included “mechanical allodynia” (2016–2019), “breast cancer” (2017–2019) and “physical exercise” (2017–2019) in the top 18 keywords (surgery, recovery,

peripheral neuropathy, exercise, peripheral nerve, neuron, sensory neuron, functional recovery, voluntary exercise, axonal regeneration, health, skeletal muscle, complication, risk, chronic constriction injury, mechanical allodynia, breast cancer, physical exercise).

Features of the 10 Most Frequently Cited Papers

The top 10 papers in terms of the quantity of citations on exercise and neuropathic pain research are shown in Table 3, and the citations of the 10 papers account for 11.43% (1074) of the total quantity of citations. The paper by Balducci et al²¹ with the title “Exercise training can modify the natural history of diabetic peripheral neuropathy” published in 2006 in *Journal of Diabetes and its Complications* was the most cited (162 citations). Among the top 10 papers, one²² was published in a journal with IF ≥ 10 (*Diabetes Care*), three^{23–25} in

Table 2 The Top 10 Authors, Co-Cited Authors, and Co-Cited References on Exercise and Neuropathic Pain Research

Author	Published Articles	Cocited Author	Cited Times	Cocited Reference	Cited Times
English AW	14	Stagg NJ	46	Stagg NJ, 2011, <i>Anesthesiology</i> , V114, P940	46
Ilha J	12	Chen YW	46	Sabatier MJ, 2008, <i>Exp Neurol</i> , V211, P489	32
Wright DE	12	Kuphal KE	44	Kluding PM, 2012, <i>J Diabetes Complicat</i> , V26, P424	32
Achaval M	10	Balducci S	44	Chen YW, 2012, <i>Anesth Analg</i> , V114, P1330	31
Chen YM	10	Cobianchi S	43	Cobianchi S, 2010, <i>Neuroscience</i> , V168, P273	30
Hung CH	9	Sabatier MJ	43	Cobianchi S, 2013, <i>Exp Neurol</i> , V240, P157	28
Navarro X	9	Gomez-Pinilla F	39	Asensio-Pinilla E, 2009, <i>Exp Neurol</i> , V219, P258	25
Sacco ICN	9	English AW	38	Allet L, 2010, <i>Diabetologia</i> , V53, P458	24
Strekmann F	9	Allet L	38	Kuphal KE, 2007, <i>J Pain</i> , V8, P989	22
Baumann FT	8	Richardson JK	37	Ilha J, 2008, <i>Neurorehab Neural Re</i> , V22, P355	22

Figure 9 The analysis of authors. Network map of active authors contributed to exercise and neuropathic pain research.

journals with $5 \leq IF < 10$ (*Anesthesiology*, *Pain*, *Journal of Pain*), three^{26–28} in journals with $3 \leq IF < 5$ (*Experimental Neurology*, *Neuroscience*) and three^{21,29,30}

in journals with $2 \leq IF < 3$ (*Journal of Diabetes and its Complications*, *Archives of Physical Medicine and Rehabilitation*).

Figure 10 The analysis of references. Co-citation map (timeline view) of references from publications on exercise and neuropathic pain research.

Top 18 Keywords with the Strongest Citation Bursts

Figure 11 The keywords with the strongest citation bursts of publications on exercise and neuropathic pain research.

Discussion

Global Trends of Exercise and Neuropathic Pain Research

This bibliometric study offers a systematic review of studies on exercise and neuropathic pain in the past 15 years. The related publications had a statistical increase with time, and the most significant growth was between 2009 and 2012. Among the five 3-year periods, 2017–2019 had the largest number of publications (221), 2011–2013 had the highest number of citations (2980) and H-index (33). These results indicate that exercise and neuropathic pain

receive increasing attention from researchers, and the papers published between 2011 and 2013 have good quality.

The top 10 journals according to the number of published papers contributed to 18.2% (123 publications) of all the publications. Among the top 10 journals, *Pain*, *PLoS One* and *Muscle Nerve* had the largest contribution in terms of the number of publications (16 papers per journal, 2.37%). *Pain* had the highest impact factor (IF 2018, 6.029). The IF of the top 10 journals were all less than 10 according to the Journal Citation Reports (2018 version).

Table 3 The Top 10 Papers with the Most Citations on Exercise and Neuropathic Pain Research

Title	First Author	Journal	IF (2018)	Year	Citations (WoS)	WoS Categories	Category Ranking
Exercise training can modify the natural history of diabetic peripheral neuropathy ²¹	Balducci, S	<i>Journal of Diabetes and its Complications</i>	2.684	2006	162	Endocrinology & Metabolism	87/145
Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model role of endogenous opioids ²³	Stagg, NJ	<i>Anesthesiology</i>	6.424	2011	132	Anesthesiology	1/31
Inflammation-induced decrease in voluntary wheel running in mice: A nonreflexive test for evaluating inflammatory pain and analgesia ²⁴	Cobos, EJ	<i>Pain</i>	6.029	2012	117	Anesthesiology; Clinical Neurology; Neurosciences	3/31 21/199 31/267
The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy ²⁹	Kluding, PM	<i>Journal of Diabetes and its Complications</i>	2.684	2012	108	Endocrinology & Metabolism	87/145
Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury ²⁶	Asensio-Pinilla, E	<i>Experimental Neurology</i>	4.562	2009	99	Neurosciences	60/267
Balance training reduces falls risk in older individuals with type 2 diabetes ²²	Morrison, S	<i>Diabetes Care</i>	15.27	2010	98	Endocrinology & Metabolism	4/145
Treadmill training promotes axon regeneration in injured peripheral nerves ²⁷	Sabatier, MJ	<i>Experimental Neurology</i>	4.562	2008	97	Neurosciences	60/267
Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: A systematic review ³⁰	Cup, EH	<i>Archives of Physical Medicine and Rehabilitation</i>	2.697	2007	90	Rehabilitation; Sport Sciences	10/65 23/83
Extended swimming exercise reduces inflammatory and peripheral neuropathic pain in rodents ²⁵	Kuphal, KE	<i>Journal of Pain</i>	5.424	2007	86	Clinical Neurology; Neurosciences	27/199 46/267
BDNF and learning: Evidence that instrumental training promotes learning within the spinal cord by up-regulating BDNF expression ²⁸	Gomez-Pinilla, F	<i>Neuroscience</i>	3.244	2007	85	Neurosciences	114/267

Among the top 10 journals, the proportion of the journals with $2 \leq \text{IF} < 5$ was 80%. In the top 10 journals, 56.25% were Q1, 12.5% were Q2 by the journal IF quartile in Web of Science. These results showed that *Pain* was the most influential journal in this research field. Although the top 10 journals did not have high IF, the IF of most journals ranked the top 50% of IF distribution. We think that this field may need some innovative and breakthrough discoveries.

According to the quantity of published papers on exercise and neuropathic pain research, the United States led the first

echelon (252), followed by Brazil (58) and China (51). The top 10 countries/regions included four Asian countries/regions, three American countries and three European countries. Figure 6 shows that the collaboration between countries/regions was extensive. A total of 1003 institutions published papers on exercise and neuropathic pain research. According to the quantity of publications, the top 10 institutions included six from the United States, two from Brazil and two from China. Less cooperation was observed among the institutions compared with the cooperation between countries. These

results indicated that the USA, Brazil and China were the main powers in this field. The top 10 institutions were mainly from the USA with the most publications. The USA, as a developed country, is at the forefront of this research.

Research Focuses on Exercise and Neuropathic Pain Studies

The most popular research field according to the subject categories of Web of Science was Neurosciences (202 publications), followed by Clinical Neurology (127 publications) and Rehabilitation (68 publications). The top 10 subject categories by the quantity of publications were Neurosciences, Clinical Neurology, Rehabilitation, Endocrinology Metabolism, Sport Sciences, Orthopedics, Oncology, Physiology, Anesthesiology and Pharmacology Pharmacy. According to the co-citation analysis of references, the largest cluster #0 was “axon regeneration,” followed by “stress” (#1), “intraepidermal nerve fiber density” (#2) and “tai chi” (#3). According to the analysis of keywords, the strongest citation bursts of keyword since 2005 was surgery and since 2006 was recovery. The keywords by the end of 2019 contained “mechanical allodynia” (2016–2019), “breast cancer” (2017–2019) and “physical exercise” (2017–2019). Studies on exercise and neuropathic pain mainly focused on rodents in the past 15 years, and the effect of exercise on neuropathic pain was confirmed in rats. Because of the multiple causes of neuropathic pain, this research area is very broad. However, these publications were mainly focused on neurosciences and rehabilitation.

Strength and Limitations

This study is the first bibliometrics analysis to evaluate global trend and development potential in the field of exercise and neuropathic pain research in the recent 15 years. The publications were searched from the SCI-Expanded of Web of Science. In order to contain more related publications and gain rich data, the publications were not limited to one academic journal. A total of 364 different academic journals with published papers on exercise and neuropathic pain research, such as *Pain*, *PLoS One* and *Muscle Nerve*, were included in our study. This research includes analysis of the quantity of publications, citations, H-index, subject categories of Web of Science, journals and collaboration analysis between countries/institutions, co-citation analysis of references/authors and analysis of keywords.

This study has several limitations. SCI-Expanded of Web of Science is the only electronic database searched, and non-English publications were excluded. Although the majority of the publications used English on exercise and neuropathic pain research, the limitation may lead to publication bias. The last limitation is that earlier publications have a higher chance of being found and cited than do recent publications. Some potentially influential publications were not cited with high citation frequency.

Conclusions

A new perspective on the trends of exercise and neuropathic pain research is provided by this study. Although this study has several limitations, it fully reveals the global trend of exercise and neuropathic pain research. The general tendency of the publications increased from 20 published papers in 2005 to 79 published papers in 2019, and statistically significant growth was observed. The USA had the greatest contribution, and *Pain* was the most influential journal in this field. Neurosciences, Clinical Neurology and Rehabilitation were the most popular subject categories in this field. The results of this study may provide researchers with useful information, such as research frontiers, potential collaborators and cooperative institutions.

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Disclosure

The authors report no conflicts of interest in this work.

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