

Bibliometric mapping of scientific research on prion diseases, 1973–2002

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Abstract

The purpose of the present study is to analyse and map the trends in research on prion diseases by applying bibliometric tools to the scientific literature published between 1973 and 2002. The data for the study were obtained from the Medline database. The aim is to determine the volume of scientific output in the above period, the countries involved and the trends in the subject matters addressed. Significant growth is observed in scientific production since 1991 and particularly in the period 1996–2001. The countries found to have the highest output are the United States, the United Kingdom, Japan, France and Germany. The collaboration networks established by scientists are also analysed in this study, as well as the evolution in the subject matters addressed in the papers they published, that are observed to remain essentially constant in the three sub-periods into which the study is divided.

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1. Introduction

Prion diseases, also called transmissible spongiform encephalopathies, are a group of diseases, both animal and human, characterized of a neuropathological spongiform change, and transmissibility. In animals include

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scrapie, bovine spongiform encephalopathy (BSE), and other diseases. In humans, Creutzfeldt–Jakob disease (CJD) and its variant (vCJD), Kuru, Gerstmann–Sträussler–Scheinker disease (GSS), fatal familial insomnia (FFI), and sporadic fatal insomnia (SFI).

The first report of animal spongiform encephalopathy dates from the eighteenth century; known as scrapie, an endemic disease in sheep with a high rate of occurrence in Iceland, its transmission was proven experimentally in 1936 (Brown, Bradley, & Cathala, 1999). BSE, an epidemic essentially affecting bovine cattle, was first detected and diagnosed in the United Kingdom in 1986. It has since been described in many countries, primarily in Europe.

In the nineteen twenties, Creutzfeldt and Jakob described a sub-acute or chronic encephalopathic process in patients (Escudero-Torreola, 2000) occurring in the population at large at a rate of approximately one per million. The syndrome began to be studied in greater depth essentially after Gajdusek's findings on kuru in New Guinea. The discovery in the sixties that the lesions caused by scrapie were similar to those found in kuru and the Creutzfeldt–Jakob disease led to rapid progress in the molecular characterisation of the agents involved and their relationship with the existence of prions (Brown et al., 1999). Epidemiological data were obtained in 1996, followed by the experimental data that established the connection between BSE and the so-called variant Creutzfeldt–Jakob disease (vCJD), transmissible to human beings via infectivity in food (Gargani, 2002).

The purpose of this paper is to analyse scientific research on prion disease encephalopathy and Creutzfeldt–Jakob disease research trends by applying bibliometric tools to the scientific literature published between 1973 and 2002 in order to determine the volume of scientific production, the countries involved, the authors working in these areas and the trends in the research subjects addressed.

2. Methodology

The period analysed, running from 1973 to 2002, was divided into three sub-periods (1973–1982, 1983–1992, 1993–2002). The data for the study were obtained from Medline, the US National Library of Medicine's (NLM) on-line PubMed service (<http://www.ncbi.nlm.nih.gov>). The information was retrieved from the NLM controlled vocabulary database (MeSH) of PubMed contents, similar to other bibliometric studies about different diseases with a great social alarm (Onyanha & Ocholla, 2005).

The query terms used were encephalopathy, bovine spongiform [MESH] OR Creutzfeldt–Jakob syndrome [MESH] OR Gerstmann–Straussler–Scheinker disease [MESH] OR insomnia, fatal familial [MESH] OR kuru [MESH] OR scrapie [MESH] OR prion diseases [MESH] OR prion [MESH] OR prion protein [MESH].

MESH term “Creutzfeldt–Jakob syndrome” is not used in the current literature on the subject. Now is preferred “Creutzfeldt–Jakob disease”.

This search strategy yielded 7808 records. Some of these records proved to be duplicated or incomplete and were deleted. The final database consisted of 7800 records, on which an analysis of all the information of bibliometric interest was conducted. Where no author affiliation information was available, the paper was looked up in the original source. Both uni-dimensional (scientific production, co-authorship index, publication subject matter) and multidimensional (analysis of co-occurrence of terms) indicators were used; the latter as a technique to explore and study the inter-relationships among authors found in the papers reviewed (Casado et al., 1997).

Multivariate analysis – multidimensional scaling and correspondence factorial analysis – was used to obtain these indicators and explore both author's collaboration networks and trends in the subjects researched during the sub-periods under consideration. Both techniques are frequent tools used in advanced bibliometric to explore and visualize information in order to mapping scientific and technological developments (Noyons & Van Raan, 1994; Van Raan, 1993). Such relational indicators identify interactions among bibliometric data while at the same time furnishing quantitative data on the structure of the relationships between the elements of the system to which they are applied (Callon, Courtial, & Penan, 1995).

However, it could be noted that such techniques have exploratory value, inasmuch as they describe data without analyzing the causes of the structures found. Moreover, their objective is to discover and show the proximity – in a space with a short number of dimensions (generally two) – between a suite of objects or

stimuli that are inter-related in multidimensional spaces of greater complexity (Greenacre & Blasius, 1994; Hair, Anderson, Tatham, & Black, 1999). The structures resulting from the analysis are graphically represented on the so-called perceptual maps that illustrate the underlying cognitive (keywords, subject classifications) or social (authors, institutions, countries) relationships, depending on the elements represented (Kopcsa & Schiebel, 1998; Tijssen & Van Raan, 1994).

In the study on the relationships between subject categories, only the terms specified in the MeSH database as indicative of the main content of the paper (i.e. those terms with an asterisk in the MeSH field) were adopted. In order to make the study more comprehensible, these terms were standardised and in some cases aggregated along the lines suggested by the experts in prion diseases.

The visualization of results in the form of “maps” based on measures of similarity between cluster analysis terms and techniques reveals the characteristics of the intellectual structure of the scientific area studied, helping to identify the patterns described by scientific activity over time (Ding, Chowdhury, & Foo, 2001; Van Raan, 2002).

In all cases the “maps” plotted as part of the results obtained in this study were discussed with experts in prion disease and validated along the lines of their criteria. This is an important aspect in the methodological approach to any bibliometric study on the development of scientific research in a given field. In this regard, the methodology followed here benefited from the criteria of experts in prion disease from the outset in a number of important respects: selection of the source of information used; formulation of the search strategy, including the definition of the search terms based on MeSH headings; selection of types of papers to be covered in the study. This co-operation with experts contributed to minimizing the criticism often leveled at bibliometric “mapping” with respect to the results, as well as the data and methods used to reach them (Cahlik, 2000; Noyons, 2001).

All statistical analyses were run with Microsoft Excel[®] and version 10.1 of SPSS[®] for Windows. The working matrices were built with Bibexcel[®] for Windows, an in-house software for bibliometrics analysis developed by professor Olle Persson and the Inforsk Research Group at Umea University, Sweden. Data were processed and indicators obtained in accordance with the methodology proposed for information metrics studies in a paper by Sanz-Casado, Suárez-Balseiro, García-Zorita, Martín-Moreno, and Lascurain-Sánchez (2002).

3. Results

3.1. Scientific production 1973–2002

Fig. 1 shows the variations in scientific production between 1973 and 2002, in comparison with the 7800 papers published and the annual increase with regard to 1973. A gradual increase in scientific production was observed from the seventies to the mid-eighties, with a steep rise at the end of that decade. Production increased very fast from 1990, with a peak in 1991, until 1996, where another sharp rise was recorded, with peaks in 1996. The number of publications grew by 94.87% between 1973 and 1982, and by 258.97% and 871.79% from 1973 to 1992 and 1973 to 2002, respectively.

3.2. Geographic distribution of scientific production

Table 1 shows the geographic distribution of scientific production in the subject areas, along with growth in absolute values and percentages in the sub-periods established. Only the percentages corresponding to countries accounting for over 1% of the papers published in each sub-period were considered. The country with highest scientific output throughout the whole period studied was the United States (USA), with 40.19% and 41.08% of the papers published in the earlier decades, and 26.73% in the third sub-period (1993–2002). But in this third decade, whilst that country's publications accounted for a smaller percentage of the total, in absolute terms the number of papers was much higher than in the two preceding periods.

The second ranking country by number of papers published in the three sub-periods was the United Kingdom (UK), with a ratio average higher than 20%. France and Japan also conducted a considerable amount of research. Whilst Japan's relative weight declined in the third sub-period, its publishing activity did not, as it

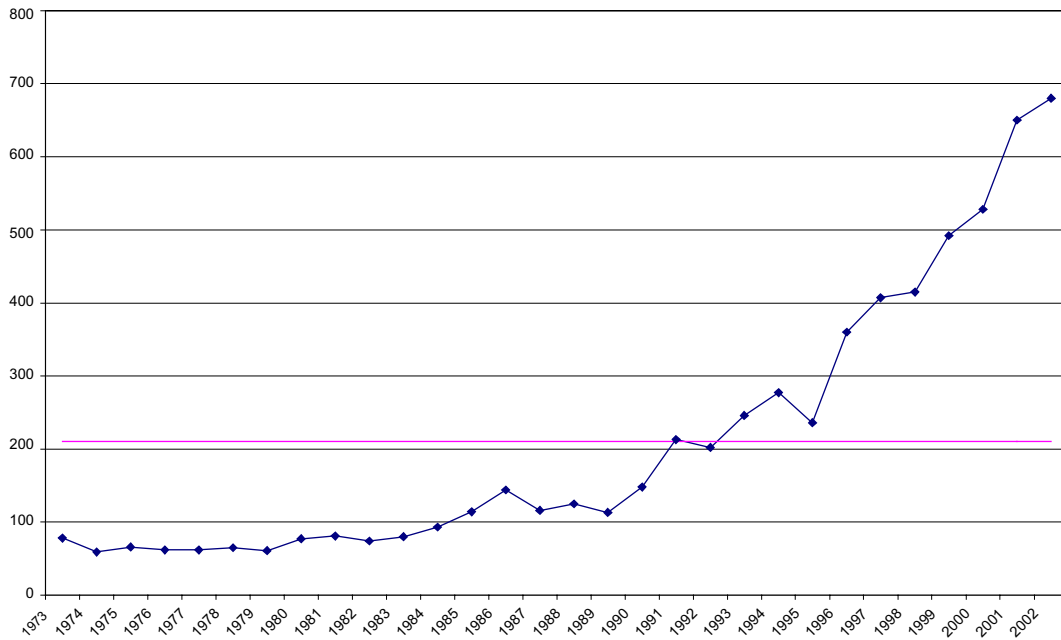


Fig. 1. Trends in scientific production, 1973–2002.

Table 1
Breakdown of scientific production by country

1973–1982			1983–1992			1993–2002		
Country	No. paper publications	%	Country	No. paper publications	%	Country	No. paper publications	%
USA	211	40.19	USA	463	41.08	USA	1087	26.73
UK	115	21.90	UK	209	18.54	UK	827	20.34
Japan	38	7.24	Japan	115	10.20	France	394	9.69
France	38	7.24	France	57	5.06	Germany	325	7.99
Italy	14	2.67	Germany	55	4.88	Japan	286	7.03
Australia	12	2.29	Italy	43	3.82	Switzerland	187	4.60
Czechoslovakia	12	2.29	Poland	31	2.75	Italy	155	3.81
Germany	9	1.71	Russia	19	1.69	Spain	74	1.82
Switzerland	9	1.71	Canada	13	1.15	Holland	72	1.77
Canada	8	1.52	Spain	13	1.15	Poland	72	1.77
Poland	7	1.33	Israel	13	1.15	Canada	59	1.45
Chile	6	1.14	Switzerland	12	1.06	Austria	58	1.43
Spain	6	1.14	Other*	84	7.45	Australia	55	1.35
Other*	40	7.62				Israel	54	1.33
						Belgium	42	1.03
						Other*	319	7.85

* Countries whose contribution accounted for less than 1% of the total.

was 2.4-fold higher in absolute terms than in the second decade. Switzerland is another case that merits mention. With a production of under 1% in the first sub-period and 1.06% in the second, it climbed to sixth place in the third, accounting for 4.6% of the total papers published.

3.3. Scientific collaboration

Scientific collaboration has been established by means of co-authorship index which shows the size of research groups and the strength of links between them. Fig. 2 shows the evolution of co-authorship index,

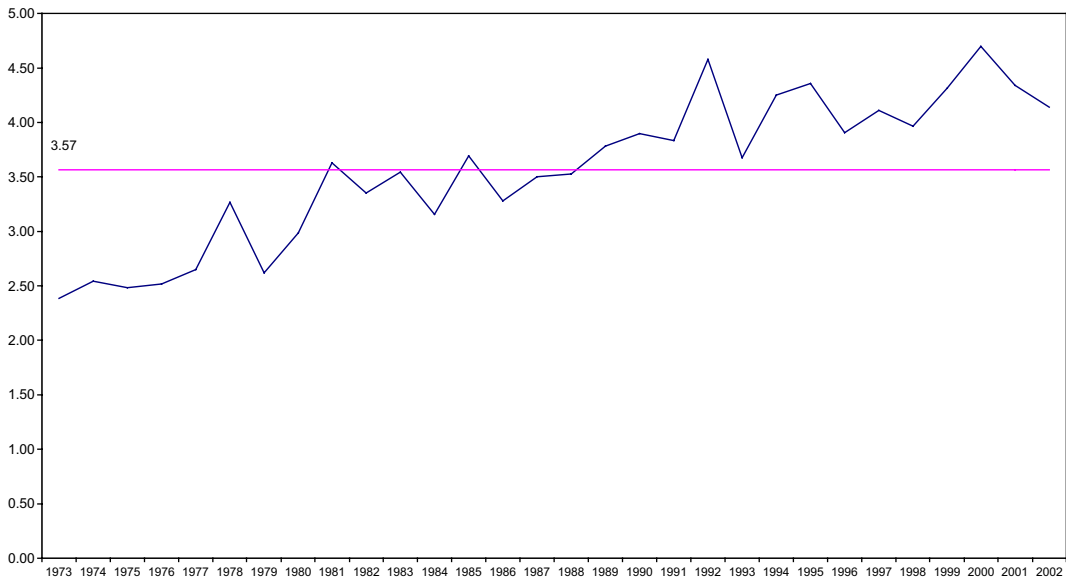


Fig. 2. Evolution of the co-authorship index.

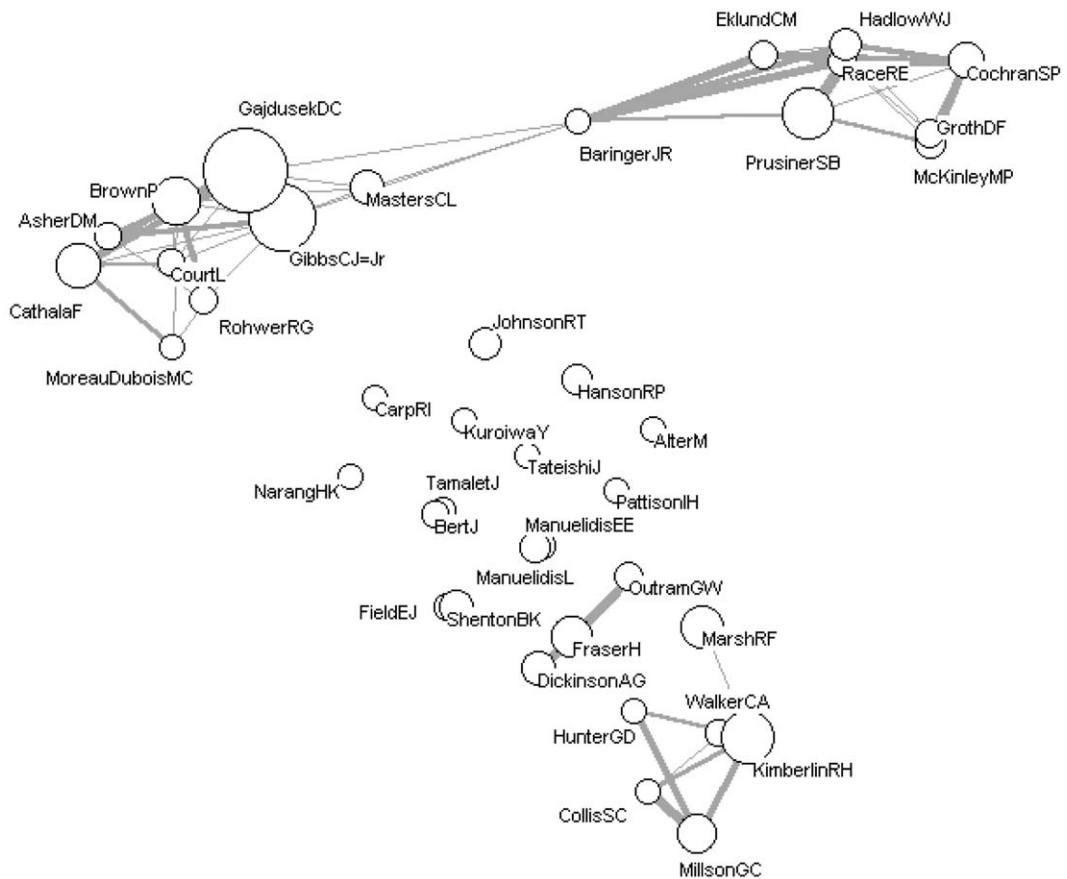


Fig. 3. Collaboration networks during the 1973–1982 sub-period.

which began at a very low value (2.3 authors per document). However, the values show an important growth from 1981 to 2002 reaching 4.14 authors per paper. Although we cannot identify a regular pattern in the evolution of co-authorship indexes, their values are higher than the average (3.57 authors per document) from 1981 to 2002.

Figs. 3–5 show the result of running multidimensional scaling technique to mapping collaboration networks in the three sub-periods established. We have considered only more productive authors (higher than 1% with regard to all papers in each sub-period).

The map for the first sub-period (1973–1982) shows three well-defined clusters: the biggest, at the top left corner, is formed by: Gajdusek D.C., Brown P., Cathala F., Gibbs C.J.Jr., Asher D.M., Court L., Masters C.L., Moreau-Dubois M.C. and Rohwer R.G.. The first four authors in this group, especially Gajdusek, are the most active one. A second cluster is at the top right corner and it is formed by: Prusiner S.B., Cochran S.P., Groth D.F., McKinley M.P. and Baringer J.R. In this case Prusiner is the most productive author. Note the position of Baringer which seems a connection between Gajdusek's cluster and Prusiner's cluster. The third cluster is located at the bottom right zone of the map. It is formed by: Kimberlin R.H., Millson G.C., Marsh R.F., Hunter G.D., Collis S.C., Hanson R.P. and Walker C.A. Other clusters on this map are shorter than the three above-mentioned ones. Note that many of them have only two authors.

The map for the second sub-period (1983–1992) shows a more complex network (Fig. 4). There are more collaboration links for this decade and some changes can be observed with regard to the period between 1973 and 1982. The first cluster, at the bottom right of the map is the most productive. It is formed by: Gajdusek D.C., Gibbs C.J.Jr., Cathala F., Brown P., Chatelain J., Asher D.M., Goldfarb L.G., Liberski P.P., Pocchiarini M.

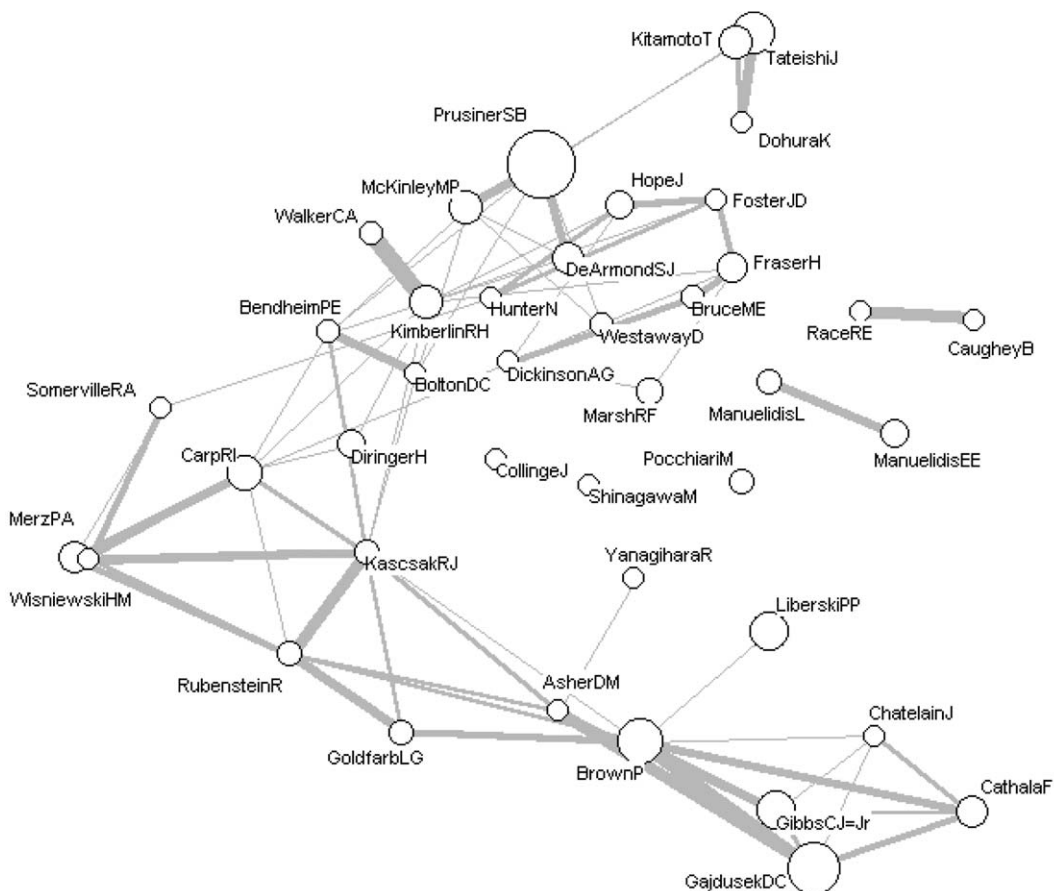


Fig. 4. Collaboration networks during the 1983–1992 sub-period.

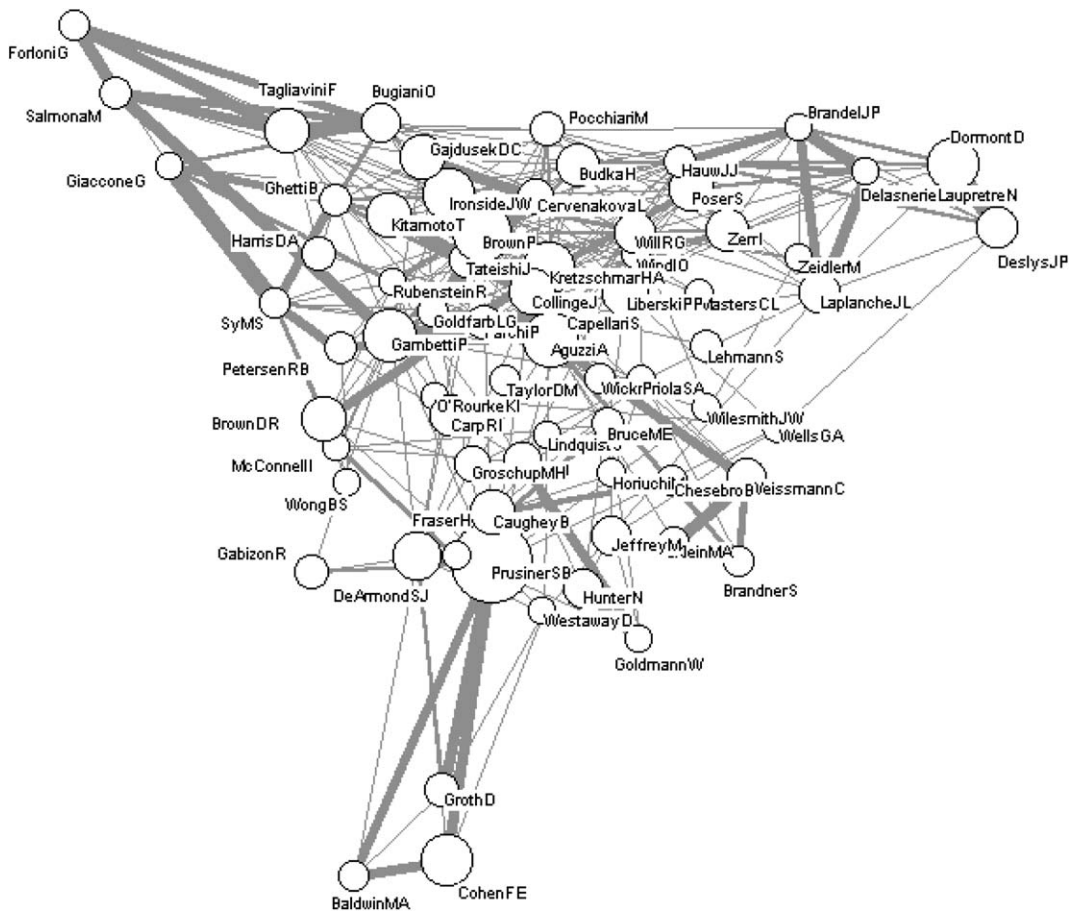


Fig. 5. Collaboration networks during the 1993–2002 sub-period.

and Yanagihara R. The second cluster situated at the top left of the map is formed by: Prusiner S.B., Bendheim P.E., DeArmond S.J., McKinley M.P., Bolton D.C., and Westaway D. Note that the group of Manuelidis E.E. and Manuelidis L. is isolated from the rest; in this sense these two authors show a similar behaviour with regard to collaboration links in the first sub-period analysed. In addition, there are two new clusters in this period, the first one formed at the left of the map by: Carp R.I., Diring H., Kasczak R.J., Kimberlin R.H., Wisniewski H.M., Rubenstein R., Walter C.A., Merz P.A., Kimberlin R.H. and Walter C.A., and the second (situated slightly above and to the right of the first) formed by: Hope J., Foster J.D., Dickinson A.G., Hunter N., Marsh R.F. and Somerville R.A. The cluster formed by Japanese's researchers Tateishi J., Kitamoto T. and Dohura K. appears at the top of the map.

The configuration of the last sub-period (1993–2002) is shown in Fig. 5. We can see important changes with regard to the size of groups and the links among them. A more concentrated network is the result of a more productive and collaborative environment. Note the growing number of clusters (12) and the increase in the “web” of links. Authors like Gajdusek, Brown and Prusiner have maintained high productive profiles and could be named “research leaders” for the three periods at all, although it is evident that they have diversified their contacts and partners for publications.

The cluster comprising authors Tateishi and Kitamoto also appears in this decade, although in this case there is no intense collaboration with other authors.

New clusters of scientific activity are found in this last sub-period, such as those formed by Will R.G., Pocchiari M., Ironside J.W. and Zeidler M., located on the upper part of the map, and Zerr I., Kretzschmar H.A., Groschup M.H., Poser S., Windl O. and Brown D.R., on the upper left. The centre of the map is

occupied by the cluster formed by Aguzzi A., Brandner S., Klein M.A. and Weissmann C. and the upper left by the cluster whose members are Bugiani O., Tagliavini F., Salmona M., Ghetti B., Harris D.A., Giaccone G., Lehmann S., Forloni G. and Collinge J.

3.4. Research trends: relation between clusters of authors and subject categories

Figs. 6–8 show the distribution of author’s clusters with regard to a group of research subjects-matters for each sub-period. Correspondence factor analysis has been used to map the relation between these two categories. The author’s clusters of each sub-period are shown in Annex 1.

Fig. 6 shows the picture for the 1973–1982 sub-period. We can appreciate some clusters close around the co-ordinate’s origin among some high productive subject-matters (i.e. scrapie, nervous system, chemicals and drugs, diseases). Note the position of cluster 1 (C1) which seems the most productive in many subjects. The position of cluster 5 (C5) suggests it is focused on Anatomy, kuru-immunology and CJD-immunology. At the centre left is the cluster 2 (C2) which seems more active in scrapie, chemicals and drugs and nervous-systems-diseases. Cluster 4 (C4) seems more focused on scrapie. Note the position of clusters 7 (C7) formed by the two isolated above-mentioned authors (Manuelidis E.E. and Manuelidis L.) which appear nearest to psychiatry and psychology and CJD-pathology.

Fig. 7 shows the picture for the second sub-period (1983–1992). An important fact is the change in position with regard to the first sub-period. Most of clusters are moving towards central zone. It could be a clue that authors are being more active in a group of subject matters. Cluster 1 (C1) is the most productive. Nearest to C1 is C5 formed by Japanese’s researchers (Tateishi, Kitamoto, Dohura) which are related to CJD-pathology. Cluster 2 (C2) located at the top side seems to be related to prions-analysis, prions-genetics and purification. Note that cluster 4 (C4) has a peripheral position, and it seems more related to subjects like CJD-metabolism.

More research is observed in this decade on prion-related subjects, some of which, such as prions > isolation and purification, qand prions > drug effects diversify and acquire a central position on the map. Most of the clusters, particularly C3 and C2, publish on these subjects.

Fig. 8 shows the situation for the last sub-period (1993–2002). We put an emphasis on this more complex picture, with a lot of clusters and subject matters very close to the barycentre. Subjects like: chemical and

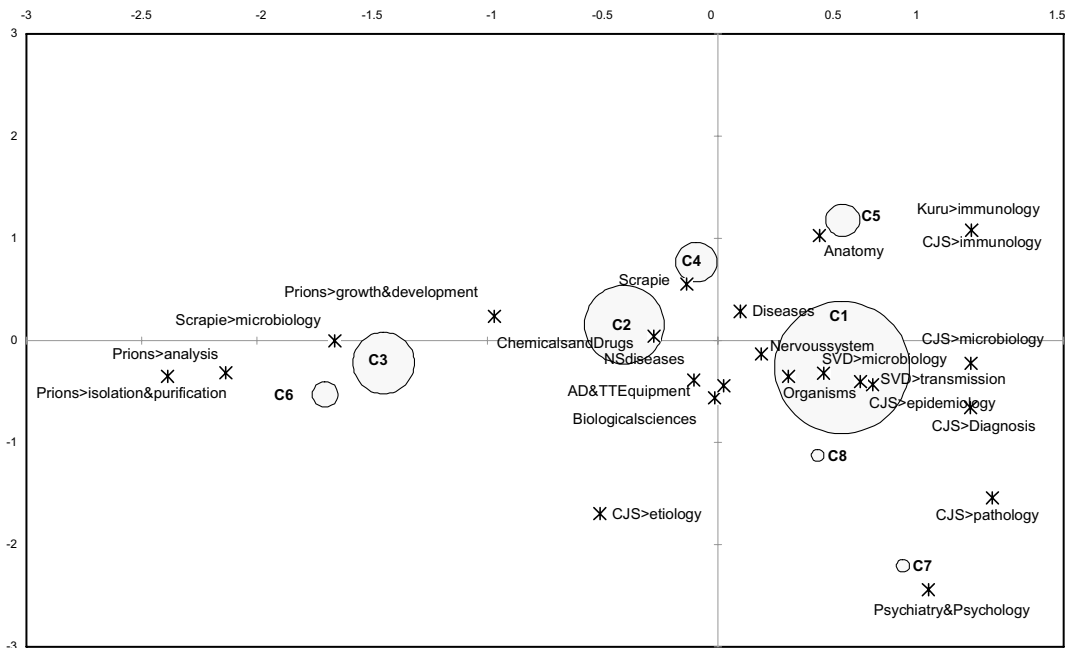


Fig. 6. Author’s clusters vs research subjects-matters (1973–1982 sub-period).

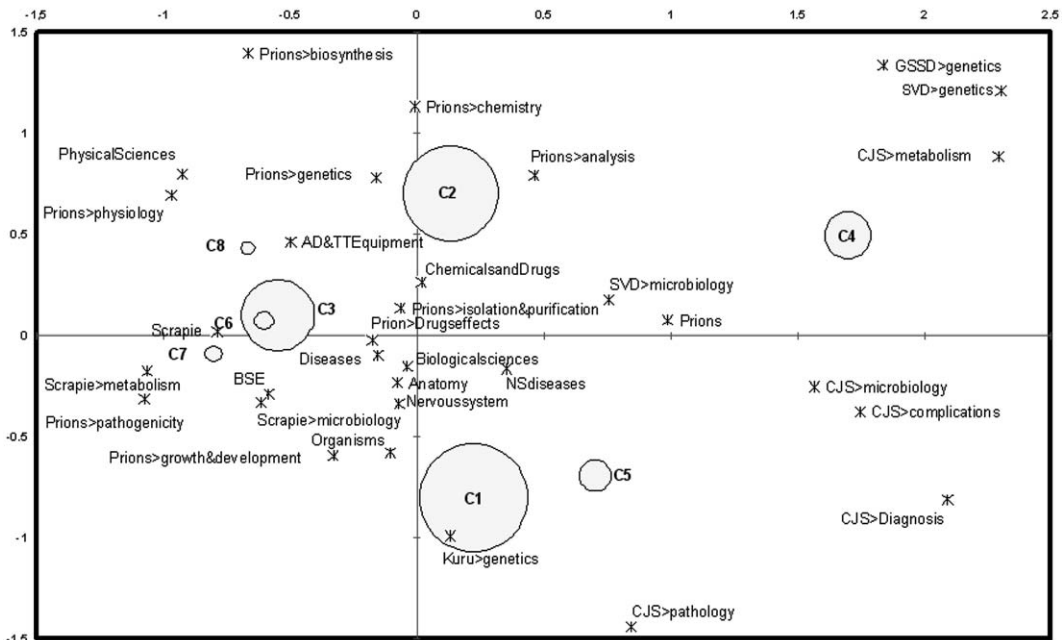


Fig. 7. Author's clusters vs research subjects-matters (1983–1992 sub-period).

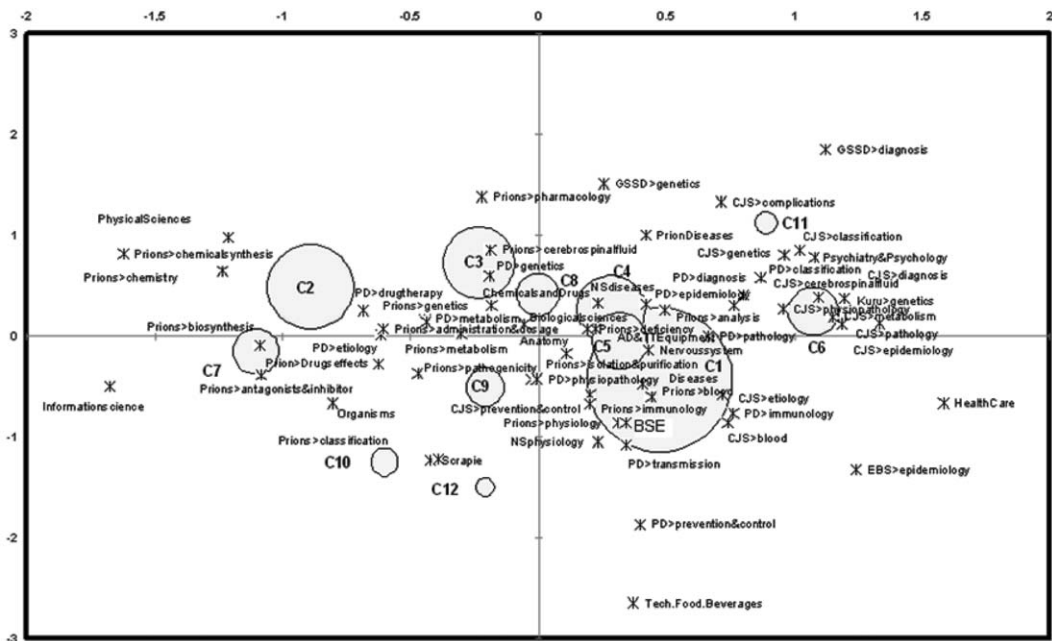


Fig. 8. Author's clusters vs research subjects-matters (sub-period 1993–2002).

drugs, nervous-system, biological-sciences, diseases, nervous-system-diseases and anatomy, seem to define the dominant trends on the map. Intense publishing activity is likewise observed in this decade, along with a considerable diversification of prion-related subjects, many of which are sited centrally on the map.

Also clusters C1, C5 and C4 appear at the right side and very close to each other. It suggests similarities in subject research profiles. At the right side are two clusters (C6 and C11) which show a publication pattern

related to some subjects in the central zone but a focus on CJD-diagnosis, CJD-epidemiology, CJD-pathology, and others. Close to the centre are three clusters (C8, C3, and C9). The profiles of these clusters are related to subjects placed in the centre but also to other topics like prion-disease-genetics, prions-pharmacology, and scrapie. Finally, shortest clusters appear at the bottom left of the map (C10 and C12). These clusters seem to be related to scrapie and BSE.

4. Discussion and conclusions

The most notable findings in the study include the fast increase of the number of publications on these subjects after 1990. With regard to the scientific activity by geographic area, greater output in other countries was responsible for the relative decline in the US production. Scientific output in the United States is characterised by intense research in nearly all areas of knowledge, possibly spurred in this case by the impact of Gajdusek's research on kuru and Prusiner's studies on prions. The United Kingdom maintains the second place by number of papers published in the three sub-periods because its output was substantially increased in the last sub-period as a result of the effect of BSE; and nearly all the victims of variant Creutzfeldt–Jakob disease were diagnosed in that country, with only approximately 5% confirmed outside the British Islands. A similar pattern was observed in Switzerland, where several cases of BSE also appeared earlier on. The rise in scientific production in countries such as Germany or Spain may have been due to the existence of CJD registries and research groups associated with diagnosis and epidemiological monitoring.

The values of co-authorship index show that scientific collaboration between the researchers has had grown significantly from 1981 to 2002 reaching 4.14 authors per paper. The collaboration networks between authors in the three established sub-periods have been very important. The map for the first sub-period (1973–1982) shows three well-defined clusters, while the map for the second sub-period (1983–1992) shows a more complex network (Fig. 4). There are more collaboration links for this decade and some changes can be observed with regard to the first one. The configuration of the last sub-period (1993–2002) shows important changes with regard to the size of groups and the links among them. A more concentrated network is the result of a more productive and collaborative environment. A large number of clusters of scientific activity on these subjects appear for the first time in this last decade, such as those formed by: Bugiani O., Zerr I., Ironside J.W., Gambetti P., or Aguzzi A. It will be noted that many of these “new” researchers are scientists working in Europe. The EU began to take an interest in prion research in the early nineties, and many scientific projects have been and continue to be implemented on the subject since the Fourth Framework Programme (1994–1998).

In relation with the subject matters that make up the clusters the authors are working on, in the first sub-period, it can be observed that there are various clusters in the central zone of the map, and that the subject matters, where more publications have taken place are scrapie, nervous system, chemical and drugs or diseases, while in the second sub-period, there is a migration of the majority of the clusters towards the central zone of the map, which indicates that there is a major coincidence in the research subjects in which they are published. Some of these subjects are the same as in the preceding sub-period (nervous-system, chemicals and drugs, disease, diseases of the nervous system or biological-sciences). Nonetheless, as a result of the intense scientific activity on prion-related subjects among most of the clusters in this decade, several of these subjects acquire a central position on the map. In 1982, Prusiner began to call the agent of diseases “prion”, and the theory of “slow virus” diseases was slowly abandoned.

In the last sub-period, it can be observed that both the number of participating clusters and the subject matters, where they are published are increasing. It is also worth mentioning that, as in the previous period, the majority of the clusters occupy a central position, because they share many of the research subjects, which are similar to those of the previous periods (chemicals and drugs, nervous-system, biological-sciences, disease, diseases of the nervous system or Anatomy). In this period, much greater diversification is observed around prion-related subjects, most of which move towards the centre of the map, having been integrated into the lines of research addressed by the clusters.

Finally, attention is drawn to the usefulness of bibliometric tools in the analysis of research activity, for the precise insight they provide into the characteristics and evaluation of scientific output. The information obtained from applying these techniques, in conjunction with expert opinion, can provide valuable support for enhanced scientific policy decision-making.

Acknowledgement

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Annex 1

Clusters and authors of the three sub-periods.

Period 1973–1982

- C1 Gajdusek D.C., Brown P., Cathala F., Gibbs C.J.Jr., Asher D.M., Court L., Masters C.L., Moreau Dubois M.C., Rohwer R.G.
- C2 Kimberlin R.H., Millson G.C., Marsh R.F., Hunter G.D., Collis S.C., Hanson R.P., Walker C.A.
- C3 Prusiner S.B., Cochran S.P., Groth D.F., McKinley M.P., Baringer J.R.
- C4 Fraser H., Dickinson A.G., Outram G.W.
- C5 Field E.J., Narang H.K., Shenton B.K.
- C6 Hadlo Wwj, Eklund C.M., Race R.E.
- C7 Manuelidis E.E., Manuelidis L.
- C8 Bert J., Tamalet J.

Period 1983–1992

- C1 Gajdusek D.C., Gibbs C.J.Jr., Cathala F., Brown P., Chatelain J., Asher D.M., Goldfarb L.G., Liberski P.P., Pocchiari M., Yanagihara R.
- C2 Prusiner S.B., Bendheim P.E., De Armond S.J., McKinley M.P., Bolton D.C., Westaway D.
- C3 Carp R.I., Diringier H., Kascasak R.J., Kimberlin R.H., Wisniewski H.M., Rubenstein R., Walker C.A., Merz P.A.
- C4 Hope J., Foster J.D., Dickinson A.G., Hunter N., Marsh R.F., Somerville R.A.
- C5 Tateishi J., Kitamoto T., Dohura K.
- C6 Bruce M.E., Fraser H.
- C7 Manuelidis E.E., Manuelidis L.
- C8 Caughey B., Race R.E.

Period 1993–2002

- C1 Brown P., Liberski P.P., Gajdusek D.C., Rubenstein R., Cervenakova L., Jeffrey M., Wells G.A., Budka H., Goldfarb L.G., Masters C.L., Carp R.I., Bruce M.E., Wilesmith J.W.
- C2 Prusiner S.B., Cohen F.E., De Armond S.J., Gabizon R., Groth D., Baldwin M.A., Westaway D.
- C3 Bugiani O., Tagliavini F., Salmona M., Ghetti B., Harris D.A., Giaccone G., Lehmann S., Forloni G., Collinge J.
- C4 Zerr I., Kretzschmar H.A., Groschup M.H., Poser S., Windl O., Brown D.R.
- C5 Laplanche J.L., Hauw J.J., Dormont D., Deslys J.P., Delasnerie-Laupretre N., Brandel J.P.
- C6 Will R.G., Pocchiari M., Ironside J.W., Zeidler M.
- C7 Caughey B., Priola S.A., Horiuchi M., Lindquist S., Chesebro B.
- C8 Gambetti P., Sy M.S., O'Rourke K.I., Parchi P., Petersen R.B., Capellari S., Wong B.S.
- C9 Aguzzi A., Brandner S., Klein M.A., Weissmann C.
- C10 Hunter N., Hope J., Goldmann W.
- C11 Kitamoto, Tateishi J.
- C12 McConnel II., Fraser H., Taylor D.M.

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