Alzheimer's Disease: The Intellectual Structure of Brazilian Research before and after the Implementation of the National Agenda for Health Research Priorities

Angelina Pereira da Silva*, Jacqueline Leta

Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, BRAZIL.

ABSTRACT

Introduction: Alzheimer's Disease, the most common type of dementia, affects mainly the elderly population and will grow significantly in the coming decades. Objectives: To investigate Brazilian scientific research on Alzheimer's Disease before and after the implementation of the National Agenda for Health Research Priorities. Methodology: A quantitative research study based on data from Brazilian scientific output on Alzheimer's Disease collected from the Scopus database in 1974-2005 and 2006-2019. Scientometric methods were used, especially journal and author cocitation analysis. Results: The findings show a growth of original and review articles on Alzheimer's Disease, published mainly in journals focused on health sciences and authored by researchers from institutions in the Southeast region. The analysis of co-citation journals revealed that Brazilian research on Alzheimer's Disease, in the first period, was distributed on 72 titles focused on health sciences and, in the second period, 679 titles with broader field coverage. The co-citation authors initially revealed 93 authors co-cited in distant clusters and, in the second period, 1,000 authors co-cited in more connected clusters. Conclusion: Attention is drawn to the strong growth in the Brazilian production of Alzheimer's Disease after the implementation of the Agenda, as well as to a change in the intellectual structure of research on Alzheimer's Disease. It is supposed that the Agenda may have acted as a vital element not only for scientific production but also for the release of resources and the participation of researchers, both fundamental actors that would also explain the observed changes. Keywords: National Agenda for Health Research Priorities, Alzheimer's Disease, Scientometrics, Cocitation journals, Co-citation authors, Intellectual structure.

Correspondence

Angelina Pereira da Silva

Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, 21941-901, BRAZIL. Email id: angelina.silva@bioqmed.ufrj.br ORCID ID: 0000-0002-3127-275X

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INTRODUCTION

Life expectancy has increased continuously over the last few decades, but with different growth rates in different regions of the planet and between men and women.^[1] The effect of this increase is the growth of the elderly population, that is, individuals over 60 years of age, as shown by data from the World Health Organization (WHO). In 2017, this population group totaled just over 920 million, which represented 13% of the world population.^[2] For the coming decades, the estimate is that there will be strong growth in this segment and that, in 2050, one person in five, that is, 20% of the world population, will be 60 years old or more. The increase in the elderly population, according to the WHO, is the result of at least two factors, the reduction in the fertility rate and the increase in life expectancy, which are more evident.

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© The Author(s). 2022 This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/ licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. Given this prospect, which points to significant growth of the elderly population in the coming decades, different nations, especially those in which this segment represents an expressive part of their current human and social capital, face the challenge of rethinking their health systems and including the aging as the pivot of their actions in the field of public health.^[2] It becomes, therefore, essential to ensure that the issue of population aging and its many ramifications, which include the diseases typical of this population segment, assume centrality in national health policy agendas.

In Brazil, in 2003 and 2004, the first priorities for health research were outlined, which were added to others and became, in 2005, the National Agenda of Priorities for Health Research (ANPPS). This instrument aims to line current health needs with scientific, technological, and innovation research activities and allocate available resources for investment in strategic research topics for the Unified Health System (SUS).^[3,4]

With more than 15 years of existence, it is relevant to question whether the ANPPS was able to mobilize the Brazilian scientific community in the effort not only to conduct but also to expand research of interest and priority for the country. Several authors understand that scientific activities must be by the country's economic, social and political objectives.^[5-7] One way to assess the impact of a given public policy on scientific activity is to survey performance indicators of authors and institutions and reveal trends and characteristics of knowledge production in the policy-related area/domain/field. Such indicators have been the theme and object of study of many disciplines, including "Sociology of Science, Philosophy of Science, History of Science and Public Policy",^[8] which, many times, are appropriate specific assessment techniques typical of bibliometrics, scientometrics, webmetrics^[9] and altmetrics.^[10]

Considering that, according to Perissé and Marli,^[11] there is a clear trend toward the expansion of the elderly population in the country, this research has as its central theme Alzheimer's Disease (AD), which is the most common type of dementia and which affects mainly this segment of the population. This disease, according to many studies, will grow significantly in the coming decades. In the United States, e.g., Hebert and collaborators^[12] found that in 2000, there were 4.5 million older adults with this disease and estimated that the number would grow to 13.2 million in 2050. In Brazil, Feter and other authors^[13] revealed that the country, in 2016, had the second-highest prevalence of dementia by age in the world, in which Alzheimer's Disease corresponded to 70% of cases and that from 2007 to 2017, there was a 55% growth in the number of deaths due to insanity. In addition, there are cases of underreporting of the disease. According to the study by Nakamura et al.^[14] the notification rate in the United Kingdom is 52% compared to 77% in Brazil.

According to experts, Alzheimer's Disease significantly alters the quality of life of individuals.^[12] The increasing presence of individuals affected by this disease increases the demand for health services, which, in turn, must be fully articulated with other actors, such as universities and research institutes, both of which are primarily responsible for conducting research and development of the (new) National System of Innovation in Health, as proposed by Gadelha.^[15]

In this sense, would the ANPPS, as a strategic part of the National Policy on Science, Technology, and Innovation in Health, have had the role of stimulating and diversifying the intellectual structure of Brazilian research on Alzheimer's Disease, a theme closely associated with the health of the elderly?

To answer the research question, the present study investigates Brazilian scientific production in two periods, before and after the implementation of the ANPPS, based on descriptive and relational indicators. This last approach is based on two cocitation analyses, making it possible to identify the intellectual structure of scientific production on Alzheimer's Disease.

Anpps and Alzheimer's Disease in the Sub Agenda Health of the Elderly

Organized by the Department of Science and Technology (Decit) of the Ministry of Health in 2005, the first ANPPS included 24 sub agendas, which represented the priority areas of research. The elaboration of this first Agenda resulted from an intense political debate and had the active and decisive participation of different professionals with different expertise, whether in health research or the health care of the Brazilian population.^[16]

The Agenda was elaborated during five consecutive stages that preceded its approval at the 2^{nd} National Conference on Science, Technology and Innovation in Health (CNCTIS) in 2005: 1) health status and living conditions, 2) definition of sub agendas in research, 3) definition of research topics, 4) public consultation and 5) 2^{nd} National Conference on Science and Technology and Innovation in Health. The final plenary of the 2^{nd} CNCTIS did not fully evaluate the sub agendas, and for this reason, the sub agendas were sent to the Plenary Session of the National Health Council, which was approved at the 151^{st} Ordinary Meeting.^[3]

The Agenda, which aimed to meet health needs and stimulate the "production of knowledge and social and procedural goods in priority areas for the development of social policies",^[17] was thus configured as a first instrument collectively built to support the National Policy on Science, Technology and Innovation in Health in the country, where health research priorities were aligned with the principles of the Unified Health System (SUS).

Next, Figure 1 presents the 24 research sub agendas of the first ANPPS.



Figure 1: ANPPS: sub agendas of health research. Source: Adapted from Brazil.^[3]

The themes of the subagendas range from broad themes, such as Clinical Research or Epidemiology, to more specific themes, some of which are aimed at vulnerable populations, such as the Health of Indigenous Peoples. It is important to highlight that each topic indicated in the subagendas can be conducted from any stage of the scientific knowledge production chain, from basic research to operational research, and may even involve human beings and methods from various areas of knowledge. It is noteworthy that the definition of the subagenda themes, which took place in 2003 at the Agenda Construction Seminar, was based on various international experiences. Based on them, a list of eight criteria was created for the definition of themes or research priorities, which includes everything from health indicators to scientific performance and social equity indicators, as reported in the ANPPS:^[3] "a) disease burden, measured by DALY (Disability Adjusted Life Years) or other indicators; b) analysis of the determinants of the burden of disease according to the different levels of intervention: individual, family, community; ministry, health system, and services; research institutions; government policies and other sectors with an impact on health; c) state of the art of available scientific and technological knowledge; d) cost-effectiveness of possible interventions and the possibility of success; e) effect on equity and social justice; f) ethical, political, social and cultural acceptability; g) possibility of finding solutions; h) scientific quality of the proposed research; i) feasibility of human and financial resources".

We are interested in sub agenda six of the first ANPPS, in other words, the one that addresses the theme or research priority Health of the Elderly. This research priority aimed at a population segment aged 60 years or older in 2017, it represented 13% of the world population, but by 2050, it is expected to reach 20%.^[2] In Brazil, according to data from the Brazilian Institute of Geography and Statistics, the expectation is even higher: 25% of our population will be elderly in 2043.^[11]

The Health of the Elderly sub agenda includes three main axes: (a) Magnitude, dynamics, and understanding of the health problems of elderly individuals, which includes research that seeks to understand the relationship between some social and economic conditions and the health of elderly individuals; (b) Understanding the mechanisms of diseases associated with the aging process, that is, research that focuses on biological mechanisms associated with the health of elderly individuals; and, finally, (c) Evaluation of policies, programs, services, and technologies, whose emphasis is on research that investigates the impact of government actions and initiatives on the health of the elderly.^[3]

For the present study, which focuses on a specific disease, Alzheimer's Disease (AD), it is understood that studies on this disease are covered in the three axes of the sub agenda. However, AD is cited on axis two, within the subaxis, which textually says "Molecular-genetic predictor markers of frailty (dementia, cardiovascular and cerebrovascular diseases, osteoporosis, Parkinson's disease, 'Alzheimer's Disease', swallowing disorders, hearing and others)".^[3] The explicit indication of this disease in axis two points to the centrality that this disease assumes (or should assume) within the research priorities of the Brazilian scientific community.

AD was identified in 1906 by psychiatrist and pathologist Alois Alzheimer and presented at the 7th Meeting of Southwest German Psychiatrists held in Tübingen, Germany and published in 1907 in the journal Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin.^[18,19] For some decades, AD was also called presenile dementia since its diagnosis was associated with symptoms of dementia in individuals between 45 and 65 years of age. Only in the late 1970s was there an understanding that the disease occurs regardless of age. It is true; however, it has a higher prevalence among elderly individuals, that is, those aged 65 and over.^[20]

It is essential to highlight that Alzheimer's Disease is a particular type of dementia, a broad term that encompasses diseases that progressively evolve and compromise mental cognitive and behavioral abilities, directly interfering with people's quality of life.^[21] The characteristic that distinguishes AD from other dementias is the increased presence of beta-amyloid and tau proteins that accumulate incorrectly in the brain, obstructing cognitive functions.^[22] It is an irreversible brain disorder associated with age that initially affects memory loss and is also associated with mental confusion, changes in behavior and personality, cognitive losses, and physical control over the body.^[22,23] There is no cure, but there are drugs that can in some cases control these symptoms and slow the progression of the disease. Qiu, Kivipelto and von Strauss^[24] highlight that etiological factors, advanced age, genetic predisposition and vascular risk factors and disorders (smoking, arterial hypertension, obesity, diabetes, and cerebrovascular lesions) contribute to the evolution of dementia and AD. In contrast, intervention factors for vascular risk control, active lifestyle, mental stimulation, and physical and social activities are essential to reduce the risk or delay the clinical development of these diseases.

Alzheimer's Disease is the most common form of dementia, accounting for 60 to 70% of cases, followed by Lewy body disease and frontotemporal dementia. According to the World Health Organization (WHO), in 2019, dementia reached 55.2 million people distributed across the Western Pacific (20.1 million), Europe (14.1 million), the Americas (10.3 million), Southeast Asia (6.5 million), the Eastern Mediterranean (2.3 million) and Africa (1.9 million). It is estimated that by 2030, this number will increase to 78 million, and by 2050, it will reach 139 million people worldwide.^[22,25] Another essential data revealed by the WHO (2021) is the measurement of data on the global burden of disease from the DALY indicator, an acronym for Disability Adjusted Life Years. In addition, the results indicate that Alzheimer's Disease and other forms of dementia were among the leading causes of DALYs in 2019. Another alarming result is that among the top 30 causes of DALYs, in the period from 2000 to 2019, AD and other dementias showed the highest rate of increase (122%). The data show that dementia, including AD, is higher for women in all regions. In 2019 alone, there were 1.6 million deaths from dementia worldwide, of which approximately 65% were women.^[25]

In Brazil, Melo and collaborators^[26] conducted a study based on estimates from The Global Burden of Disease (GBD) 2016, demographic data, and national health data to determine the burden of AD and other dementias in the Brazilian population aged 60 years or over between 2000 and 2016 in the country. To express the multiplicity of the disease burden distributed across the five regions, data from two states in each region with the highest number of ages were considered according to the 2010 census. The results showed a 7.8% increase in the prevalence in this group of AD and other dementias: from 961.7 to 1,036.9 per 100,000 people. In addition, these diseases ranked fourth place among the leading causes of death in this population segment in the country and moved to second place in 2016.

Intellectual Structure and Co-citation Analysis

The development of a scientific study demands the consultation and appropriation of knowledge from the literature on a specific issue. In this process, citation highlights are.

For Meadows,^[27] the practice of referencing previous works has become consolidated as a mechanism to ensure credit and accountability for information that supports or is contested in each work. White^[28] understands that this mechanism is configured both as a rhetorical instrument, which researchers use to support their ideas and research results, and to convince (or persuade) readers of the validity of their findings and as a legitimate means of acknowledging the accurate intellectual contributions.

In this last aspect, White and Griffith^[29] claimed that, in the early 1970s, some studies shed light on a new way of analyzing cited references: the co-citation technique. Among these studies is the work developed by Small and Griffith,^[30] in which the authors point out that this technique allowed the visualization of what they called the structure of scientific literature. A few years later, several authors, including White and Griffith,^[28] appropriated this concept and adapted it to the intellectual structure. The cocitation technique in bibliometric studies has its origins in the pioneering study by Small.^[31] According to this author, this technique, by identifying pairs of documents that appear in the reference list of a third document, allows visualizing pairs of documents with different amounts of ties. The central idea is that the greater the number of ties between two documents cited together, i.e., cocited, the greater the similarity of content between them. Thus, the technique shows document groupings or, ultimately, content groupings that represent the specialties that give structure to a given group of scientific documents.

The relationship between the co-citation technique and the concept of intellectual structure has been frequently investigated in international literature^[32-35] as well as in national literature.^[36-40]

For this research, the concept of the intellectual structure was adopted as initially proposed by White and Griffith,^[29] which gains more technical contours in the study conducted by Machado,^[41] in which the author states that intellectual structure deals with the "structure visualized from the degree of similarity of content (research topic, school of thought, methodological approach, results), which, when assembled in clusters, shows areas of expertise as well as their interconnections".

In bibliometric studies, the intellectual structure has been observed from one of the three typologies of co-citation analysis: (a) document co-citation analysis, devised in 1973 by Small and Marshakova in independent ways,^[41] (b) author cocitation analysis, elaborated by White and Griffith in 1981,^[29] (c) journal co-citation analysis, proposed by Katherine W. McCain in 1991,^[42] and document category co-citation analysis, proposed by Moya-Anegón and collaborators in 2004.^[43]

Figure 2 shows the schematic representation of the cocitation analysis, where A and B (which can be documents, authors, journals, or categories) are the items measured and visualized in the maps.

Therefore, we are interested in the techniques of author cocitation and journal cocitation analysis, upon which the intellectual structure of Brazilian scientific production on Alzheimer's before and after the implementation of the ANPPS will be discussed.

Author cocitation has as its unit of analysis the authors of the cited references and aims to identify the pairs of authors that appear cited together in a third document. The technique allows visualizing, then, the relationship between the cited authors and identifying central and peripheral authors with similar patterns that can be expressed by theoretical and/or methodological aspects in their publications, thus recognizing



Figure 2: Schematic representation of cocitation. Source: Garfield.^[44]

the intellectual structure of a knowledge area.^[41;45,46] Similarly, the journal cocitation technique emerges as an alternative to investigate the intellectual structure of a given field, but this time through pairs of journals cited together in a third paper.

METHODOLOGY

The methodological proposal of the present study is based on the understanding that Scientometrics is a field dedicated to the "study of the measurement of scientific and technological progress".^[47] Thus, the research is quantitative in nature,^[48] based on descriptive and relational analyses of the journal and author cocitation.

The field of study is the Brazilian scientific production on Alzheimer's Disease, and the studied population are the original and review articles. Considering scientific journals as the main channel for scientific dissemination, the choice of these types of documents is justified by understanding that original articles are publications that present "original themes or approaches" and review articles by being a "type of study on a given subject in which information already published is summarized, analyzed and discussed".^[49,50]

To achieve the intended objectives, the methodology comprised the three main stages, as presented below.

To define the search strategy, on November 11, 2020, it performed a query on Medical Subject Headings (MeSH) to identify all terms associated with Alzheimer's Disease. The 34 terms obtained in the MeSH were used in the data collection, performed on November 11, 2020, in the Scopus database, a multidisciplinary, referential, and abstracted, restricted-access database, edited by Elsevier, of the Brazilian production on Alzheimer's. The search strategy used the title, abstract, and keyword fields and considered the terms: "alzheimer's disease" OR "dementia, senile" OR "senile dementia" OR "dementia, alzheimer type "OR "alzheimer type dementia (ATD)" OR "dementia, alzheimer-type (ATD)" OR "alzheimer type senile dementia" OR "primary senile degenerative dementia" OR "dementia, primary senile degenerative" OR "alzheimer sclerosis" OR "sclerosis, alzheimer" OR "alzheimer syndrome" OR "alzheimer dementia" OR "alzheimer dementias" OR "dementia, alzheimer" OR "dementias, alzheimer" OR "senile dementia, alzheimer type" OR "acute confusional senile dementia" OR "senile dementia, acute confusional" OR "dementia, presenile" OR "presenile dementia" OR "alzheimer disease, late onset" OR "late onset alzheimer disease" OR "alzheimer's disease, focal onset" OR "focal onset alzheimer's disease" OR "familial alzheimer disease (FAD)" OR "alzheimer disease, familial (FAD)" OR "alzheimer diseases, familial (FAD)" OR "familial alzheimer diseases (FAD)" OR "alzheimer disease, early onset" OR "early onset alzheimer disease" OR "presenile alzheimer dementia".

For this step, the following filters were used: a) affiliation country: Brazil, and b) document type: original articles and review articles. The filter for the year of publication was not used since the aim was to check the year when the studies on Alzheimer's started in the country. However, articles with publication years of 2020 and 2021 were excluded since 2020 was still in progress at the time of data collection, and the periodicity of publication of the journals varies (weekly, every two weeks, monthly, etc.), consequently impacting the search results and the analysis of the results of this research.

A total of 2,630 articles (2,035 original and 595 review articles) published from 1974 to 2019 were retrieved. The information associated with these articles was downloaded in CSV, containing the following fields: information on citations, bibliography, abstract and keywords, and references. The data were analyzed with Excel and Vosviewer software, version 1.6.15, April 2020.

To elaborate on the journal cocitation graphs, we considered a) the type of analysis was cocitation and the analyzed unit was the cited sources, b) the counting method was fractional, c) generated a thesaurus to standardize the journal titles, and d) the minimum number of citations of the cited source was 20, as suggested by the software, resulting in 3,276 sources and 72 thresholds in the 1974-2005 period and 23,814 sources and 681 thresholds in the 2006-2019 period.

To verify the correct form of the abbreviated title, we consulted the following databases: a) Ulrichsweb - A restricted-access information source edited by ProQuest, it has coverage in more than 900 subjects, collects information from 300,000 periodical publications, such as academic journals, peer-reviewed titles, trade journals, newspapers, newsletters, etc., and provides data such as ISSN, publisher, language, subject, abstracts and indexing, full-text database coverage, among others; b) NLM Catalog - National Library

of Medicine (NLM) Catalog - It assembles bibliographic data from periodicals, books, audiovisuals, etc. Available from https://www.ncbi.nlm.nih.gov/nlmcatalog. After creating the thesaurus, at this stage, book and serial titles that were in the list of journal titles were excluded in the Vosviewer.

To identify the knowledge areas of the journal sets, the scope of the journal titles informed in the information sources Ulrichsweb, NLM Catalog, in the subject field, or on the journal website itself, in the scope category, were considered.

To elaborate on the authors' co-citation graphs, we took the following parameters: a) the type of analysis was co-citation, and the unit analyzed was the cited authors, b) the counting method was fractional, c) generated a thesaurus to standardize the authors' names, and d) the minimum number of citations of the cited source was 20, the number suggested by the software, resulting in 22,932 authors and 93 links in the 1974-2005 period and 218,883 authors and 4,112 links in the 2006-2019 period. Because the number of authors in the second period was considered the number indicated by the software with the highest total link strength. In this case, it analyzed 1,000 authors.

At this stage, to check if the abbreviated variation corresponded to the same author (for example: 'de felice, f. g.' e 'felice, f. g.'), the Web of Science database was consulted in the 'Search by beta author' option, and Scopus was consulted in the 'Authors' tab. Both present the record with author data, name entry variations and institutional links. Additionally, consulted the Google and Google Academic meta searchers engines. The second option searched the author's name between double quotation marks. The search result shows a list with the publications of the searched author. By clicking on the hyperlinked author's name, it was possible to view the institutional link, the list of papers published by year, and the citations received; in Orcid (Open Researcher and Contributor ID), unique digital identifier, free, that distinguishes name variations by a single numerical code; and in OCLC WorldCat Identifier, an Online Computer Library Center (OCLC) catalog, free, for identification of authors, name variations and list of scientific production. For some authors, it was not possible to identify one of the prenames (for example: Marshal F. Folstein).

RESULTS AND DISCUSSION

The results are presented in two sections: the first one seeks to characterize the growth and profile of journals that publish original and review articles with authors indicating at least one address in Brazil and with authors from other affiliations, called here world publications on Alzheimer's Disease, and the second one focuses on the intellectual structure of Brazilian scientific production. The analyses consider two moments of the production of Alzheimer's Disease, until 2005, that is, since the first record on this theme in the Scopus database, including the year of the implementation of ANPSS, and from 2006 to 2019, from this public policy. The justification for analyzing the production data on Alzheimer's Disease in these two moments is due to the main objective of the study, which is to investigate the Brazilian scientific production on Alzheimer's Disease before and after the implementation of the National Agenda for Health Research Priorities, i.e., to identify whether this policy was, in fact, able to guide the Brazilian scientific community toward the research of interest and priority for the country.

Growth of production, most relevant journals and institutions

Initially, we performed an analysis of the total number of original and review articles on Alzheimer's Disease with addresses in Brazil and the world, that is, original and review articles with no address in Brazil (Table 1). It is important to note that the Scopus database covers information on Alzheimer's Disease before 1974. However, for this study, we considered the production from 1974, the year of the first record of Brazilian production on the subject.

Considering the year 2005 as the landmark of the ANPPS implementation, starting in 2006, there was an expressive growth in Brazilian original and review articles, which began to represent more significant fractions within the world total: 2.15% for original articles on Alzheimer's in the Scopus database, against 0.47% in the previous period, and 2.06% for review articles, as opposed to 0.59%.

From this result, we identified the ten journal titles that published the most original and review articles, with at least one address in Brazil, on Alzheimer's Disease in the period from 1974 to 2005, i.e., before the implementation of the ANPPS, and from 2006 to 2019, after the implementation (Table 2).

From the list in Table 2, it can be observed that there was, among the most relevant journals for the theme, growth in the number of articles published between 1974–2005 and 2006–2019, from 117 to 512. Considering the total number of Brazilian original and review articles (Table 1) published

Table 1: Articles with Brazilian and worldwide affiliations in the Scopus
database on Alzheimer's Disease by period.

Period	Brazil (A)		World (B)*		A/B (%)	
	Original articles	Review articles	Original articles	Review articles	Original articles	Review articles
1974-2005	220	55	46.382	9.368	0,47%	0,59%
2006-2019	1.815	540	84.452	26.221	2,15%	2,06%

Source: Research data (2020).

* Represents the totals of Scopus articles on Alzheimer's Disease without the totals of Brazilian articles.

Table 2: Ten journals with the highest number of original and review articles on Alzheimer's Disease with Brazilian affiliation in the Scopus database in the periods 1974-2005 and 2006-2019.

Journal	1974- 2005	Journal	2006- 2019
Arquivos de Neuro Psiquiatria	47	Dementia e Neuropsychologia	140
Revista de Psiquiatria Clínica	uiatria 22 Arquivos de Neuro Psiquiatria		86
Revista Brasileira de Medicina	10	10 Journal of Alzheimer's Disease	
Brazilian Journal of Medical and Biological Research	urnal of 09 International Biological Psychogeriatrics ch		39
Jornal Brasileiro de Psiquiatria	06	Current Alzheimer Research	34
Alzheimer Disease and Associated Disorders	er Disease and 05 ed Disorders	Plos One	34
International Journal of Geriatric Psychiatry	al of 05 Revista de Psiquiatria try Clínica		30
Revista Brasileira de Neurologia	05	Frontiers in Aging Neuroscience	28
Acta Neurologica Scandinavica	04	Revista Brasileira de Psiquiatria	25
Gerontology	04	Jornal Brasileiro de Psiquiatria	23
Original articles	91	Original articles	419
Review articles	26	Review articles	93

Source: Research data (2020).

in the ten journals with the highest number of articles on Alzheimer's Disease, the fraction that these totals represent for the totals of Brazilian articles in each period was reduced from 42.5% to 21.7%, suggesting that scientific production on the subject is more diffuse in the second period.

Regarding the scope and coverage of the journals, in the first period, there was a higher frequency of journals centered on clinical medicine with a focus on psychiatry and neurology; however, there were also journals in the areas of medicine, biology, gerontology and geriatrics. Furthermore, two titles have been discontinued, four titles are open access, and four are restricted access, of which six are national titles, two from the United States, one from England, and one from Switzerland. In the second period, there is a change in the profile of the journal titles, and most of them are from the biomedical field. Seven titles are open access (five from Brazil, one from Switzerland, and one from the Netherlands) and three restricted titles (the Netherlands, England, and the United Arab Emirates).

Still within the descriptive context of the scientific production of original and review articles on Alzheimer's disease, Table 3 presents the ten Brazilian institutions that most contributed to this production in the two periods. Table 3: Ten Brazilian institutions with the highest number of original and review articles on Alzheimer's Disease with Brazilian affiliation in the Scopus database in 1974-2005 and 2006-2019.

Brazilian institutions ¹	1974 – 2005	Brazilian institutions	2006-2019
USP	104	USP	703
UFRJ	53	UFRJ	323
UNIFESP	32	UFMG	240
UFRGS	23	UNIFESP	226
UNICAMP	15	UFRGS	201
UFMG	12	UNICAMP	140
PUC-RS	09	UFSC	109
UERJ	08	UNESP	101
UPE	08	UNB	75
UFCE	07	PUC-RS	70
Total articles	271		2.188

Source: Research data (2020).

¹One can see that the contribution of the ten Brazilian institutions that published the most between the two periods went from 271 to 2,188 articles, a remarkable growth, especially if one considers the thirteen years of the second period against the 31 of the first. However, it should be noted that these totals do not allow us to infer the absolute fraction of the production that is distributed among the ten institutions because two or more of these institutions may share authorship of the same article, thus suggesting that these totals may be underestimated. Another characteristic revealed is that in the first period, the production was mainly concentrated in the Southeast region of the country, distributed in six institutions among them, three from the state of São Paulo, two from Rio de Janeiro, and one from Minas Gerais, followed by two institutions in the Northeast region (Pernambuco and Ceará) and two in the South region (Rio Grande do Sul). In the second period, the configuration presents itself differently: the two institutions from the Northeast are no longer present, and in their place are two institutions, one from Santa Catarina and the other from Brasília. Of the ten institutions listed, the Southeast continues to present itself as the region with the highest number of the most productive institutions.

It is worth highlighting the role of the *Universidade de São Paulo* and the *Universidade Federal Rio do Janeiro*, which appear in first and second place, respectively, in both periods. Last, it is also worth noting that, except for the *Pontifícia Universidade Católica do Rio Grande do Sul*, the result points to public universities as 'centers' of knowledge production about Alzheimer's Disease.

¹ Universidade de São Paulo (USP); Universidade Federal do Rio de Janeiro (UFRJ); Universidade Federal de São Paulo (UNIFESP); Universidade Federal do Rio Grande do Sul (UFRGS); Universidade Estadual de Campinas (UNICAMP); Universidade Federal de Minas Gerais (UFMG); Pontificia Universidade Católica do Rio Grande do Sul (PUC-RS); Universidade do Estado do Rio de Janeiro (UERJ); Universidade de Pernambuco (UPE); Universidade Federal de Santa Catarina (UFSC); Universidade Estadual Paulista (UNESP); Universidade de Brasília (UNB).

The intellectual structure

To identify the central journal titles to the conceptualtheoretical structure of Brazilian Alzheimer's research, the analysis considered the two moments, as presented in Figure 3A, with the cocited journals listed in the articles from 1974 to 2005, and Figure 3B, in those from 2006 to 2019. The size of the nodes is relative to the number of occurrences of each journal. Hence, the larger the number of occurrences, the larger the node size and the association between them. Each



Figure 3: Journal cocitation of the Brazilian scientific production indexed in Scopus on Alzheimer's Disease from 1974 to 2005 (A) and from 2006 to 2019 (B). Source: Research data (2020).



Figure 4: Author cocitation of scientific production indexed in Scopus on Alzheimer's Disease from 1974 to 2005 (A) and from 2006 to 2019 (B). Source: Research data (2020).

color represents a cluster: in Figure 3A, five clusters were found, while in Figure 3B, there were six.

From 1974 to 2005 (Figure 3A), i.e., before the Agenda was implemented, we find 72 titles of journals cited, organized into five groupings. In this period, as described below, the intellectual structure of research on Alzheimer's Disease was concentrated in the health sciences, with titles in the medical field specializing in neurology and psychiatry. Furthermore, only one national title stands out, Arquivos de Neuropsiquiatria, with 95 occurrences. The red cluster, the largest of which with 33 journal titles, shows a composition of journals from clinical medicine, with emphasis on the specialties of neurology and psychiatry, and with the journal Neurology taking the lead in terms of occurrence (553). The green cluster, with 21 titles, shows a composition closer to neuroscience, i.e., it has journals that are at the interface between the specialty of neurology and biosciences; the Journal of Neuroscience (184) and Journal of Neurochemistry (163) are the most prominent. With 13 titles, the blue grouping is the most generic, with prominent multidisciplinary journals such as Nature, Science, and also the Proceedings of the National Academy of Sciences of the Table 4: Foreign and Brazilian authors with more occurrences in the cocitation map of Brazilian scientific production in Scopus on Alzheimer's Disease from 1974 to 2005 and 2006 to 2019.

1974 a 2005					
Cluster	Total authors	Foreign author with the most occurrences	Brazilian author of most occurrences		
Red	42	Fostein, M.	Nitrini, R.		
Green	19	Selkoe, D. J.	Ferreira, S. T.		
Blue	10	Saunders, A. M.	Zatz, M.		
Yellow	7	Maelicke, A.	Albuquerque, E. X.		
Lilac	7	Medina, J. H.	Izquierdo, I.		
Light blue	5	Neary, D	-		
Coral	3	Kelly, J. W.	Silva, J. L.		
2006 a 2019					
Cluster	Total authors	Foreign author with the most occurrences	Brazilian author of most occurrences		
Red	422	Wang, Y.	Izquierdo, I.		
Green	253	Cummings, J. L.	Nitrini, R.		
Blue	203	Blennow, K.	De Souza, L. C.		
Yellow	112	Selkoe, D.J.	De Felice, F. G.		
Lilac	10	Borroni, B.	Gattaz, W. F.		

Source: Research data (2020).

United States of America, which has an expanded scope in the health field. Finally, the yellow cluster (with four titles) and the lilac cluster (with one title) do not show a defined profile, as they include a small number of journals.

In the period from 2006 to 2019 (Figure 3B), with the implementation of the Agenda, the intellectual structure of Alzheimer's Disease presents a different configuration from the previous period, expanding the coverage of journal titles in other areas of knowledge, with 679 journals cited (943% increase), distributed in six clusters (one more than the previous period) and with 15 national journal titles.

The red cluster is the largest, with 293 titles. This cluster is close to the green cluster in the previous period, i.e., from the field of neuroscience (between clinical and biosciences), highlighting the Journal of Biological Chemistry with 2,633 occurrences. The green cluster, with 229 titles, shows a similar composition to the red cluster of the previous period, but proportionally, it lost space to the red one in the network structure. In this cluster, we find titles in the field of neurology, psychiatry and geriatrics and among these titles, the journal Neurology has the highest number of occurrences (4,057). The red cluster has also generalist titles such as the Lancet (1,033), Jama (582) and Plos Med (63).

The blue cluster, which in the previous period had a more generic or multidisciplinary profile, is now more related to biosciences, containing the journals Journal of Medicinal Chemistry (670) and the European Journal of Pharmacology

(618) as the ones with the highest occurrences. The yellow cluster, with 25 titles, previously did not show a defined area profile; in this period, it is formed by titles focused on neurobiological and neuropharmacological aspects, and the journals Journal of Neuroscience (2,933), Neuron (1,217) and Neuroscience (1,093) were the titles with the highest occurrence. Such titles were in the green group in the previous period, suggesting that this first group, still small at the beginning, has strengthened and, in the most recent period, has configured itself as a more prominent and independent group. The lilac (15 titles) and light blue (1 title) clusters are new in this period from 2006 to 2019. A significant part of the lilac group comprises titles with coverage in neuropathology, but there are also titles with coverage in neurobiology and psychiatry. The journal Neurobiology of Aging: age-related phenomena, neurodegeneration and neuropathology stands out with 2,209 occurrences. Lastly, the light blue cluster has only two titles in health sciences, with coverage specifically in neurology.

Once we identified the changes in the pattern of journals that provide theoretical conceptual support for Brazilian research in Alzheimer's Disease, we decided to turn our attention to the authors cocited from publications from 1974 to 2005 (Figure 4A) and from 2006 to 2019 (Figure 4B). The size of the nodes is proportional to the number of occurrences of the authors.

A first observation that repeats in the previous graphs (Figure 3A and 3B) concerns the density that increases considerably between the first and second period.

In the authors' analysis, the first period found 93 cocited authors (Figure 4A), distributed in seven clusters, while in the second period, there were 1,000 cocited authors (Figure 4B) distributed in five clusters.

Unlike what was observed in the journals, the analysis of author cocitation did not reveal expressive variations in the occurrence of cocited authorships, which can be seen by the size of the nodes.

For the period from 1974 to 2005, we observe distant groupings, some of them with a small number of authors, such as the coral grouping. The red cluster has the most authors (n=42), while the coral cluster is the smallest (n=3). In this period, the author with the highest number of occurrences is Edson Xavier Albuquerque (128), who appears in the yellow grouping. A Brazilian with operations in the United States and experience in the field of toxicology, he was head of the Division of Translational Toxicology at the School of Medicine, University of Maryland, Baltimore, developing basic and translational research on the effects of chemicals on human health, including pesticides, hormones, and heavy metals. He passed away in 2018.

In the second period, the clusters are more connected and closer together. As in the previous period, the red cluster has the most authors (*n*= 422), while the lilac cluster, new in this period, is the smallest with 10 authors. Another Brazilian, this time with Brazilian affiliation, Ricardo Nitrini, is the author with the most occurrences (859). He is a CNPq research productivity fellow and full professor of neurology at the *Universidade de São Paulo* School of Medicine. In the late 1980s, he created the Group of Cognitive and Behavioral Neurology of the Hospital das Clínicas. In 2003, together with other professors from this institution, the Reference Center for Cognitive Disorders at the Clinics Hospital was created. He is a member of the multidisciplinary research group on the neuropathology of dementia. In addition to research activities, he is dedicated to teaching neurology and neuropsychology.

For a better understanding of the graphs, Table 4 was prepared, with the indication of the authors, foreign and Brazilian, with the most significant number of occurrences in each grouping and period.

In the first period, we identified those linked to American institutions among the foreign authors with more occurrences in the author cocitation network: (a) Marshal F. Folstein, professor at Tufts University (Boston, USA), conducts research in neuropsychiatry, Alzheimer's disease, and disability research; (b) Dennis J. Selkoe, deputy director of the Department of Neurology at Brigham and Women's Hospital (Boston, USA), is dedicated to using molecular approaches and related basic biological questions to study Alzheimer's Disease and Parkinson's disease; (c) Ann Marie Saunders, professor at Duke University (North Carolina, USA), conducts research on the molecular genetics of Alzheimer's Disease, with an emphasis on the identification and characterization of genetic susceptibility genes for late-onset disease; (d) Jeffery W. Kelly, professor at the Scripps Research Institute (California, USA), studies the understanding of protein folding, misfolding, and aggregation and the development of chemical and biological strategies to ameliorate diseases caused by misfolding or protein aggregation.

Additionally, among the foreigners, we find that German Alfred Maelicke, who died in 2017, was co-founder and director of Galantos Pharma, a pharmaceutical company focused on developing drugs for neurodegenerative diseases, such as Alzheimer's dementia; the Argentine Jorge Horacio Medina, professor at the *Universidaded de Buenos Aires* (Argentina), who has been conducting studies focused on memory formation, expression, and persistence; and the Englishman David Neard, researcher at the Manchester Center for Clinical Neuroscience (England), where he is developing studies on neurological diseases.

Among the Brazilians, authors associated with institutions in São Paulo and Rio de Janeiro predominate. In this group, we find (a) Ricardo Nitrini, already mentioned in this section, who works at USP; (b) Sergio Teixeira Ferreira, full professor at the Universidade Federal do Rio de Janeiro, with experience in the areas of biochemistry, biophysics, neurobiology, and interest in the study of neurodegenerative diseases, especially Alzheimer's disease; (c) Mayana Zatz, full professor at the Universidade de São Paulo, who develops research in human and medical genetics and molecular biology with a focus on neuromuscular diseases, aging in addition to research on stem cells, zika, cancer, and genetic variability associated with COVID-19; (d) Jerson Lima da Silva, full professor at the Universidade Federal do Rio de Janeiro and coordinator of the Jiri Jonas National Center for Nuclear Magnetic Resonance, where he develops research in the field of structural biology, protein folding, viral assembly and in the understanding of the mechanisms responsible for protein misfolding, which are essential in many human diseases, including cancer, prion diseases, and Parkinson's disease.

Two authors were found outside the SP-RJ axis. One of them is Ivan Antônio Izquierdo, who died in 2021, an Argentinean naturalized Brazilian who since 2004 was a full professor at the *Pontificia Universidade Católica do Rio Grande do Sul*, where he coordinated the Memory Center, a national reference in research on the cellular, molecular and pharmacological mechanisms involved in mnemonic processing. The second author is Edson Xavier Albuquerque, a Brazilian deceased in 2018, working in the U.S. for years and has been introduced previously.

In the second period, among the foreign authors, Dennis J. Selkoe, associated with the Brigham and Women's Hospital (in Boston, USA), remains on the list of authors with the highest occurrence of cocitation. In this period's list, American scientists are still in the majority, including (a) Yalin Wang, associate professor at Arizona State University (USA), conducting research in the areas of computer vision, neuroimaging, geometry and topology, and machine learning, and (b) Jeffrey Lee Cummings, professor, and director of the Chambers-Grundy Center for Transformative Neuroscience at the University of Nevada (Las Vegas, USA), conducting research in neuroscience, neurodegenerative diseases, Alzheimer's disease, drug development, clinical trials, and neurotherapeutics. Two other foreigners close this list: Kaj Blennow, professor at the University of Gothenburg (Sweden) and pioneer in developing biomarkers for Alzheimer's disease, and Barbara Borroni, professor at the University of Brescia (Italy), where she conducts research in neurology.

Among Brazilian authors, we note that, from the previous list, Ivan Antônio Izquierdo and Ricardo Nitrini remain the authors with the highest occurrence, but in different

groupings. The other three names, all from institutions in the Southeast region, are (a) Leonardo Cruz de Souza, professor at the Universidade Federal de Minas Gerais, acting in the field of cognitive and behavioral neurology, focusing on neuropsychological and biological markers of neurodegenerative diseases (frontotemporal dementia and its interfaces with amyotrophic lateral sclerosis and Alzheimer's Disease), (b) Fernanda Guarino De Felice, professor at the Universidade Federal do Rio de Janeiro, where she conducts research on the neurobiology of Alzheimer's Disease and the connection between Alzheimer's Disease and diabetes, and (c) Wagner Farid Gattaz, professor at the Universidade de São Paulo and coordinator of research in the areas of psychiatric treatment and rehabilitation, pharmacotherapy, pharmacogenetics, and neuroscience, notably in the cases of depression, schizophrenia, and Alzheimer's Disease.

CONCLUSION

The results of the present study, which sought to investigate Brazilian scientific production on Alzheimer's Disease before and after the implementation of the National Agenda for Health Research Priorities, suggest, albeit preliminarily, that this policy positively impacted scientific research on this theme. This observation is based on two sets of analyses considering the data before and after implementing this policy.

In the first set of analyses, the expressive growth in the number of Brazilian articles on AD stands out, but significantly the real increase that this production represented within the Scopus database. It is true that in the 2000s, Brazilian scientific publications indexed in international databases, such as Scopus, grew at a faster pace than those from other countries.^[51,52] Such growth has been explained by different reasons that include the growth and higher qualification of human resources acting in Science and Technology (S&T) activities in the country and the qualification of Brazilian journals that became part of the collections of international databases in greater numbers, starting in 2007.^[53] However, this growth that occurred in Brazilian scientific production as a whole was also observed for the production of a specific theme, in this case, Alzheimer's disease.

Nevertheless, in this first set, we observe a change of structural nature: the emergence of open access titles. This change may reflect a greater adherence of Brazilian research to open access journals, which was shown by Dias and contributors^[54] when analyzing a set of publications listed in Lattes.

In the second set of results, based on the two cocitation analyses, we observe changes in the intellectual structure of DA research, both from the journals and from the cocited authors. In the first analysis, we verified densification of the network, the result of a more significant occurrence of journal titles, which was also reflected in a broadening of the areas of knowledge that support DA production from 2006 to 2019. In this period, some changes in the composition of the clusters are evident, with emphasis on the formation of the yellow group, which now includes journals oriented toward neurobiology and neuropharmacology content.

In the author cocitation analysis, we also observed, in the period from 2006 to 2019, a densification of the network, resulting from a higher occurrence of cocited authors, but this did not increase the number of clusters. This finding indicates that the set of cocited authors, i.e., those who provide theoretical support to produce DA, interact more with each other and may be closer in terms of areas of knowledge. A closer look at the most frequently occurring cocited authors shows that those with US affiliation predominate among the foreign authors, while those from the Southeast region predominate among the Brazilian authors, mainly with affiliation in São Paulo. The strong presence of authors linked to institutions located in the State of São Paulo is in line with the extensive literature dealing with indicators of Brazilian science.[53,55,56] It is also relevant to highlight the presence of Brazilians as coauthors since the first period, but the list of these authors in the second period went through a significant renovation, including a young researcher, Fernanda Guarino de Felice, who became an exponent of the intellectual structure of scientific production in DA.

Considering the main results of this study, pointed out above, and continuing the research, as the following steps, it is intended to carry out complementary analyses, which include, for example, the analysis of scientific production on AD from countries with similar performance to Brazil in neuroscience, as indicated in the study by Chitra and Jeyshankar,^[57] which will allow identifying whether the changes found in this work are specific to Brazilian scientific production or if it is a global trend. Finally, this study plans to conduct interviews with Brazilian and international experts and, thus, complementing the quantitative analyses, we will have more evidence of whether and how a State policy, the ANPPS, has boosted production in the area. Therefore, the data set may reveal helpful information for the various actors of Science and Technology (S&T), contributing, including the maintenance of resources for scientific research activities, technology, and innovation in strategic themes, especially in the health field.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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