Alzheimer´s Disease Research: A Network Science Approach

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ABSTRACT

A limit number of studies have applied bibliometric visualisation to explore the network structure of Alzheimer's Disease (AD). This paper uses CiteSpace, Carrot and VOSviewer to analyse and visualise the intellectual structure of AD, characterizing, quantitatively and qualitatively, the global scientific outputs, and identifying their trends. The 9,753 articles obtained from the science citation index expanded database (SCI-E), from Web-of-Science, were analysed. The publication data is analysed computationally to identify publication patterns, a rate of growth of publications, types of authorship collaboration, the most productive authors, countries, institutions, journals, keywords, the citation and keyword patterns, the hotspots and the areas of research on the AD. The paper presents a detailed analytical mapping of AD research and charts the progress of discipline with various useful parameters. The authors expect to contribute to the theory, supplying researchers with new tools and enabling practitioners to improve their knowledge about the AD evolution and trends.

Keywords: Bibliometric analysis; Scientific outputs; Alzheimer; Keywords analysis; Collaboration network; Research trend.

1. Introduction

Alzheimer´s Disease (AD), first defined by Alois Alzheimer, a German psychiatrist and neuropathologist in 1907 (Zilka and Novak, 2006), is the most common form of dementia in the elderly (Berr et al. 2005, Cummings 2004). AD is a progressive neurodegenerative disorder characterized by deterioration of cognitive and functional capacities and several neuropsychiatric and behavioral symptoms (Jalbert et al. 2008). The risk of dementia grows exponentially with age (Ziegler-Graham et al. 2008). While dementia shortens the lives of those affected, its greatest impact is upon the quality of life, both of those living with dementia, and their family and caregivers (Prince et al. 2015). Close to 50 million people worldwide are currently living with dementia, and this number is projected to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 (Prince et al. 2015). By 2050, there is expected to be one new case of AD every 33 seconds, or nearly a million new cases per year, and AD prevalence is projected to be 11 million to 16 million in United States (Alzheimer's Association 2012). Dementia also has a huge economic impact. The worldwide cost associated with this increasing dementia prevalence is expected to rise from the current $818 billion to $2 trillion by 2030 (Prince et al. 2015). Given the unprecedented personal, societal, and healthcare costs, it is not surprising that global efforts to develop and implement dementia risk reduction strategies are occurring (Greenwood and Parrott 2017**).**

Bibliometric methods have been used through the publication of subject categories, institutes, journals, and countries (Sakai et al. 2011), or by the citation analysis (Wen and Huang 2012). To identify the trends of the theme, the distribution of keyword in different period provides more information than the changes in publications and citations (Li et al. 2009; Mao et al. 2010; Wang et al. 2013). There are few bibliometric studies investigating AD (Chen et al. 2014; Clive et al. 2003; Sorensen 2009) and are lacking specifically a quantitative and qualitative simultaneously analysis of publications, citations, journals, countries, institutions, authors, keyword and trends. That lack of knowledge offered to the authors a study field contributing to the bibliometric methodology identifying the global AD research, the hot issues and trends during the period of 1997 till September 2017. This would help researchers to improve their performance by realizing the all-around insights into the current state of global AD research and the establishment of further directions. Bibliometric analysis is now firmly established as scientific specialities and are an integral part of research evaluation methodology especially within the scientific and applied fields (Ellegaard and Wallin, 2015). Following the same authors, the use of bibliometric methods is obviously

driven by a need to evaluate scientific production and making the results available to policymakers, scientists or other stakeholders. Researchers become aware of the new trends, competing groups and possibilities for scientific cooperation (Barth, Haustein, and Scheidt, 2014). The analytical mapping can answer the following research questions about AD:

- What are the main areas and documents of research?
- How research publications have grown over time?
- In which countries and institutions most of the research work has been done?
- What are the top publication sources?
- Who are the most productive and more cited authors?
- What are the collaboration of authors, countries and institutions?
- What are the hot issues and trends observed?

Our paper identifies the course of development and analyze different aspects of AD research. The results obtain a useful overview and understanding of this field from 1997 to the current state of art. To the best of our knowledge, this work is the first of its kind. The rest of the paper is organized as follows: Section 2 describes the material and methods used. Section 3 presents the analytical results. Finally, Section 4 concludes with a summary of the work, its usefulness and limitations.

2. Material and methods

The following dimensions were selected as a basis to measure the global research in AD: publications, citations, journals, keywords, countries, authors, institutions, research areas and trends. The underlying data originate in the tabulation of each dimension came from the online version of science citation index expanded database, from the Institute of Scientific Information Web-of-Science database (WoS). The WoS is a leading and frequently used metric of science accomplishment in most fields of human creativity (Li et al. 2009). Since January 1997 until 25 October 2017, there were 134,637 documents with keywords: Alzheimer and Alzheimers in the topic field of AD, distributed through 145 areas, where the top 5, corresponding to 96.4% of all AD research, are represented in. Fig 1: Neurosciences Neurology (46.7%), Biochemistry Molecular Biology (13.6%), Geriatrics Gerontology (13.3%), Psychiatry (10.1%) and Pharmacology Pharmacy (9.8%).

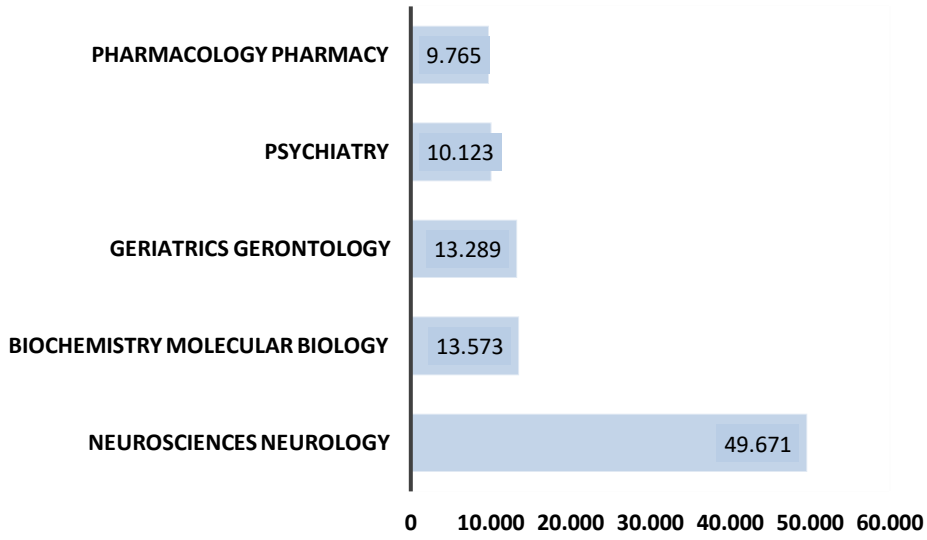


Fig.1: Percentage of research areas of Alzheimer disease extracted from SCI_E.

From those WoS areas, the authors selected for the study "Geriatrics and Gerontology", filtering the analysis to 17,114 documents. Within the WoS references obtained, the focus of our research are articles (9,753), which constitute 57% of the document type (Fig.2).

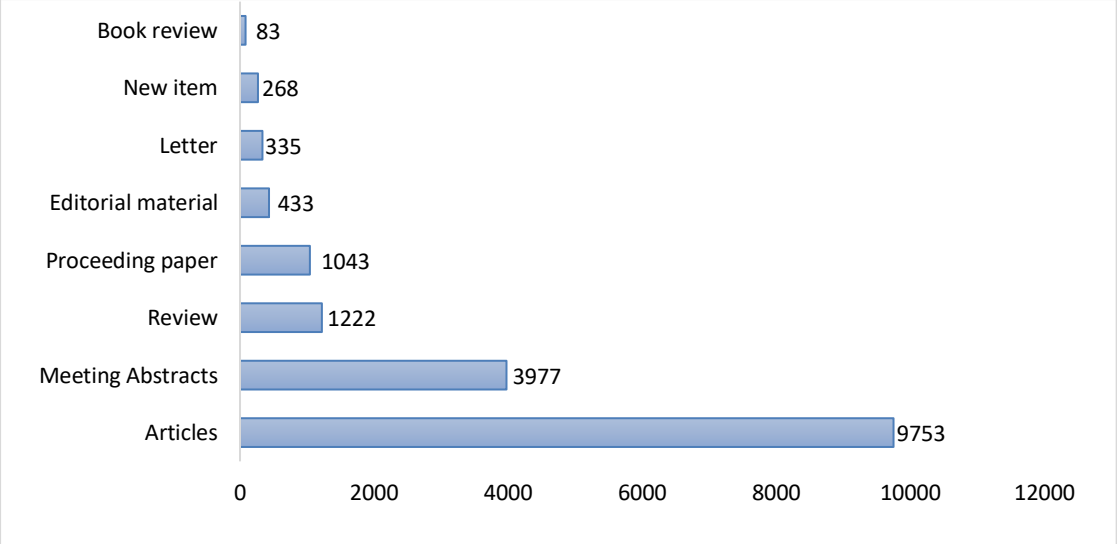


Fig.2: Document type extracted from Web-of-Science during 1997-2017 on Alzheimer Disease.

To provide more scientific and accurate information about Alzheimer disease research, only articles with the search keywords in the front page were searched out for further analysis (Fu et al. 2012). The most cited articles should have at least a total of 100 citations in the surveyed period (Chuang et al. 2011), originating for the present research 610 highly cited articles.

The global scientific outputs were generated using CiteSpace (http://cluster.cis.drexel.edu/~cchen/citespace/), Carrot (http://search.carrotsearch.com/carrot2-webapp) and Vosviewer

(http://www.vosviewer.com/). The method to evaluate the global research in Alzheimer disease is shown in Fig.3.

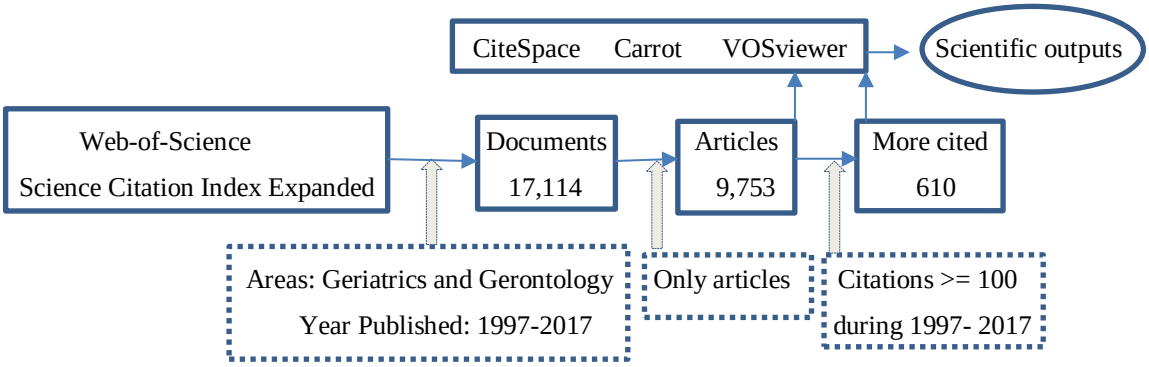


Fig.3: Method to evaluate the global research in Alzheimer disease.

The scientific output includes publications, citations, journals, keywords, countries, authors, institutions, research areas and trends. Collaboration and contributions of different countries and institutions were estimated by the affiliation of at least one author to the publication.

3 Results and Discussion

3.1 Temporal evolution

There has been an increase in the number of Alzheimer disease publications from 1372 during 1997-2001, to 3959 during 2012 till September 2017. Over the past 20 years, the number of articles increases steadily in the period 1997-2011, and a remarkable growth was observed afterwards. The growing trend indicated that increased attention has been paid to Alzheimer disease research (Fig.4). Although the number of citations is higher than the publications, it showed a decreasing trend after 2006. Each publication is read on average 40.8 times during 1997-2001, increasing to 44.3 times during 2002-2006. Afterwards, there is a decreasing to 25.6 times during 2007-2001, and to 7.12 times in the last period. The last result is expected because more recent publications have less opportunities to be cited than older ones. Moreover, the last period of research occurred from 2012 until 20 of October 2017.

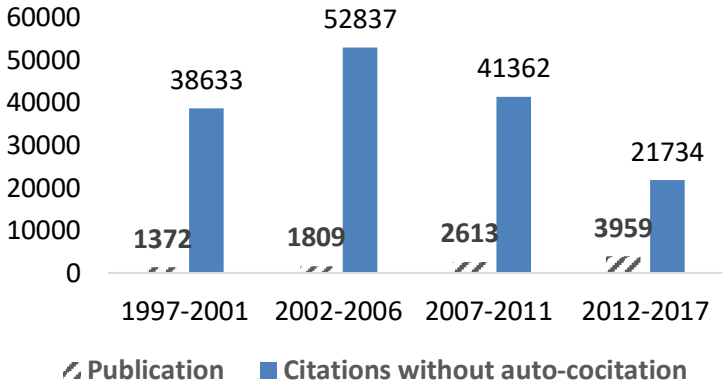


Fig.4: Trends in publications and citations of Alzheimer disease, 1997-2017.
Search results from SCI-E.

The analytical methodology used by the authors involve computing different indicators as defined in standard bibliometric literature. The main indicators include TP (total number of publications), TC (total number of citations), Average Citations Per Publication (ACPP), Relative Growth rate (RGR) and Doubling Time (DT), which measure the time required for the number of publications in a certain year to become double. ACPP is defined as: A$CPP = TC/TP$. According to Mahapatra (1985), the rate of growth with respect to time and doubling time are defined as follow, where Ni and Ni-1 are the number of publications in the years i and $i-1$:

$$RGRi = \ln(N_i) - \ln(N_{i-1})$$

$$DTi = ln2/RGRi$$

The authors have computed the parameters RGR, DT and ACPP (Table 1). AD has now emerged as is a wide research area, with applications into different domains. The results show that RGR has the highest value (0.8) in 2002-2006. The mean of RGT indicates a relative rate of growth of 0.7 for the period. A DT value of 1.1 indicates that the number of research publications is doubling in 1.1 years time, which is an indicator of a very rapid growth in the amount of work being done on this domain.

Table 1: Year-wise output and growth pattern.

Years	TP	TC	TC without auto-cocitation	h-index	Mean of Citations	Cumulative	RGR	DT
1997-2001	1372	56028	38633	105	40.8	1372	0.0	0.0
2002-2006	1809	80102	52837	115	44.3	3181	0.8	0.8
2007-2011	2613	66834	41362	89	25.6	5794	0.6	1.2
2012-2017	3959	34412	21734	52	7.1	9753	0.5	1.3

Search results from SCI-E and from the authors (2017)

3.2 Leading Journals

Research articles on Alzheimer disease appear in 501 journals included in WoS. The major journals have at least 100 citations per publication (Chuang et al. 2011). Therefore, within this threshold, Table 2, ordered by citations, shows 17 most productive journals in AD which published 8260 or 85% of the total papers and received 7447 citations or 7.1% of the total 105,195 citations. The h-index is used to find which source has the largest number of high-quality publications in AD field. Neurobiology of Aging, from England, with an impact factor (JIF) of 5.117 in 2016, published the largest number of high quality papers in Alzheimer disease. In fact, this journal has the highest h-index (139), published 2106 papers that received 78039 citations in other publications. Journals of Gerontology Series A- Biological Sciences and Medical Sciences from USA, has the highest impact factor (5.957), while Psychogeriatrics, from Japan has the lower impact factor (1.693) of these top journals. The USA has a top ranking with six journals, followed by England with four journals in AD research. Journals that have impact factors in 2016 superior to 4.0 account for 30% of the publications, while journals with less than 4.0 account for 46% of the publications.

Table 2: The most active journals in Alzheimer disease research, 1997-2017

Source Titles	Country	Publications	Citations	h-index	JIF 2016
Neurobiology of Aging	England	2106	78039	139	5.117
Dementia and Geriatric Cognitive Disorders	Switzerland	1174	31772	78	3.511
International Journal of Geriatric Psychiatry	England	803	25394	79	3.087
Journal of The American Geriatrics Society	USA	400	20466	86	4.388
American Journal of Geriatric Psychiatry	USA	439	14351	61	2.868
International Psychogeriatrics	USA	473	7453	43	2.423
Experimental Gerontology	England	206	6124	56	3.340
Journal of Geriatric Psychiatry and Neurology	USA	222	5093	44	2.109
Journals of Gerontology Series A- Biological Sciences and Medical Sciences	USA	167	4852	44	5.957
Aging & Mental Health	England	219	3808	35	2.658
Mechanisms of Ageing and Development	Switzerland	106	3269	39	3.087
Journal of Nutrition Health & Aging	France	184	3138	31	2.772
American Journal of Alzheimers Disease and Other Dementias	USA	312	2602	25	3.018
Archives of Gerontology and Geriatrics	Ireland	206	2348	30	2.086
Frontiers in Aging Neuroscience	Switzerland	270	1801	32	4.504
Geriatrics Gerontology International	Japan	76	695	17	2.351
Psychogeriatrics	Japan	113	664	17	1.693

Search results from SCI-E; JIF = Journal Impact factor in 2016

The journal impact factor (JIF), commented before, is represented in Fig.5, where the greatest impact is marked with bigger circular shape.

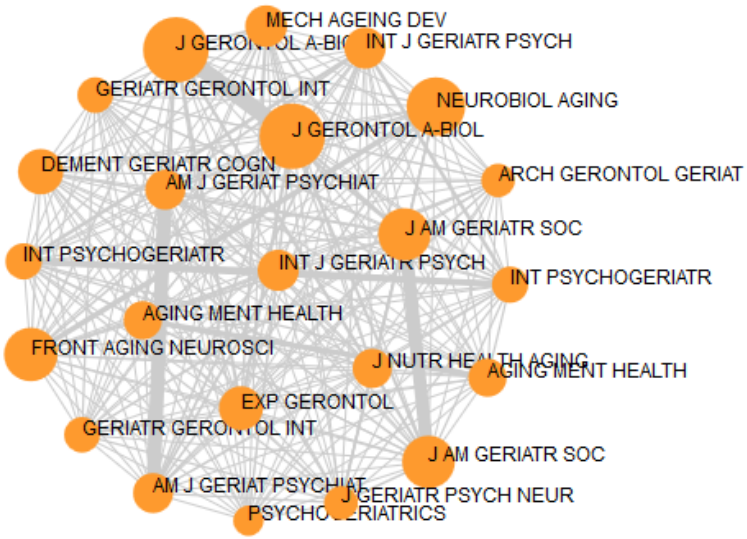


Fig.5: Visualization of the Journals Impact Factor of Alzheimer disease, 1997-2017. Search results from SCI-E

3.3 Country, Institution and Author Analysis

3.3.1 Country Analysis. Amongst 93 countries, there are 31 that have published more than 50 publications which had more than 100 citations in Alzheimer disease research, during 1997-2017, listed in Table 3. The USA accounts for the largest number of 3,499 publications and 114,585 citations, followed by England (889 publications, 25,975 citations), Italy (771 publications, 19,316 citations) and Germany (601 publications, 17,316 citations). Domination in publication is not surprising from these mainstream countries since this pattern occurred in most scientific fields, showing a correlation between investigation and Gross Domestic Product (Zhou and Zhao 2015).

VOSviewer was used to represent the collaboration between countries that have produced more than 5 documents and have more than 5 citations in the period. The items are groups by cluster and then listed alphabetically within each cluster. There were 54 countries that meet these thresholds, which have been aggregated into 7 clusters of research collaboration in AD research, shown in Table 2. Cluster 1 shows that USA collaborate with more 17 countries, including mainly Australia, Brazil, Peoples R China, South Korea and Taiwan. The proportion of citations per publication were also calculated. In Slovenia (cluster 3) each paper is on average cited 76.0 times, while in Malaysia (cluster 1) each paper is cited 5.6 times. TP is the total publications; TC is the total citations, and ACPP is the average number of citations per publication.

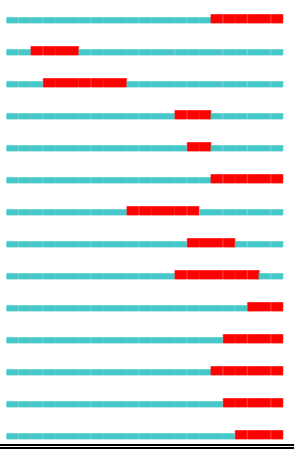
Table 3: The most active countries in Alzheimer disease research and clusters of research collaboration, 1997-2017.

Clusters	TP	TC	ACPP	Clusters	TP	TC	ACPP
Cluster 1 (18 items)				Cluster 3 (9 Items)			
Usa	3499	114585	32.7	Czech Republic	30	428	14.3
Japan	531	9575	18.0	Hungary	27	779	28.9
Peoples R China	437	6034	13.8	Luxembourg	5	186	37.2
Australia	381	9454	24.8	Norway	98	2323	23.7
South Korea	207	3781	18.3	Romania	9	108	12.0
Brazil	125	2518	20.1	Russia	25	405	16.2
Taiwan	117	1627	13.9	Saudi Arabia	9	196	21.8
Ireland	77	2597	33.7	Slovenia	7	532	76.0
India	62	860	13.9	Sweden	498	15702	31.5
Singapore	50	771	15.4				
Argentina	32	757	23.7	Cluster 4 (7 Items)			
Chile	24	280	11.7	England	889	25975	29.2
Mexico	20	253	12.7	Finland	148	4935	33.3
Egypt	15	332	22.1	Greece	83	1908	23.0
Thailand	14	269	19.2	Wales	68	2012	29.6
Colombia	13	162	12.5	Poland	65	1230	18.9
South Africa	7	163	23.3	Scotland	62	1363	22.0
Malaysia	5	28	5.6	North Ireland	34	1201	35.3
Cluster 2 (9 Items)				Cluster 5 (4 Items)			
Germany	601	17316	28.8	Switzerland	224	6029	26.9
France	472	11641	24.7	Israel	113	2595	23.0
Netherlands	392	11366	29.0	Turkey	72	799	11.1
Spain	341	6537	19.0	Portugal	48	941	19.6
Belgium	144	4105	28.5				
Austria	74	1946	26.3	Cluster 6 (3 Items)			
Iceland	10	255	25.5	Canada	510	16825	33.0
Bulgaria	7	180	25.7	Denmark	108	3040	28.1
Estonia	5	257	51.4	Iran	13	70	5.4
				Cluster 7 (2 Items)			
				Italy	771	19316	25.1
				New Zealand	23	480	20.9

Search results from SCI-E and CiteSpace

Burst detection using SCI-E and CiteSpace can identify countries emerging over time, having statistically significant fluctuations on the citation count, during a short period of time (Table 4). The time interval is depicted as a blue line. The period time in which a country was found to have a burst is shown as a red line segment, indicating the begin year and the ending year of the duration of burst. Prior to 2012 the burst countries were Japan, Israel, Norway, Ireland and Singapore. The emerging countries nearby 2017 are People's Republic of China, at the top list, with strength of 521.564, with a period of burst between 2013-2017; followed by Russia, Portugal, Taiwan, Chile, Iran, Colombia and Argentina.

Table 4: Emerging and burst countries in Alzheimer disease research during 1997-2017.

Countries	Strength	Begin	End	1997 - 2017
Peoples R China	521.564	2013	2017	
Japan	93.236	1998	2001	
Israel	70.333	1999	2005	
Norway	70.039	2010	2012	
Ireland	60.631	2011	2012	
Russia	48.159	2013	2017	
Singapore	47.887	2006	2011	
Wales	43.839	2011	2014	
Portugal	41.609	2010	2016	
Taiwan	40.702	2016	2017	
Chile	33.038	2014	2017	
Iran	32.819	2013	2017	
Colombia	32.105	2014	2017	
Argentina	3.289	2015	2017	

Search results from SCIE and CiteSpace

3.3.2 Institution Analysis. Overall 6581 institutions have published scholarly publications related to Alzheimer disease. The top 50 institutions, having more than 50 publications and 750 citations, are represented in Table 5, all playing an important role in the research activities of AD. There is the predominance of institutions of USA. Univ California Los Angeles (cluster 2) has the highest number of publications (219) and citations (12126).

Table 5: Top institutions in Alzheimer disease research during 1997-2017.

Cluster	TP	TC	Cluster	TP	TC
Cluster 1 (18 Items)			Cluster 2 (17 items)		
Karolinska Inst	213	6761	Univ Calif Los Angeles	219	12126
Kings Coll London	133	3023	Johns Hopkins Univ	174	5473
UCL	122	3051	Univ Washington	143	6354
Univ Gothenburg	100	3762	Univ Pittsburgh	140	4595
Vrije Univ Amsterdam	93	2103	Univ Calif San Diego	138	5043
Univ New S Wales	88	2286	Univ Calif San Francisco	134	4400
Univ Cambridge	84	2538	Univ Penn	118	4195
Univ Milan	82	2393	Mayo Clin	116	4430
Inserm	76	2121	NIA	105	4196
Kuopio Univ Hosp	76	3152	Univ Kentucky	99	5232
Univ Manchester	76	2244	Stanford Univ	82	2638
Univ Melbourne	72	2553	Rush Univ	77	2444
Univ Oxford	69	2510	Univ Calif Irvine	70	3665
Univ Barcelona	68	1595	Indiana Univ	63	1941
Tech Univ Munich	64	1781	Univ Michigan	62	1906
Lund Univ	63	1615	Univ Calif Davis	54	1987
Newcastle Univ	56	757	Univ Minnesota	54	2152
Univ Bonn	55	1688			
Cluster 3 (10 Items)					
Harvard Univ	140	5079	Cluster 4 (4 Items)		

Duke Univ	111	4295	Univ Toronto	134	3095
Columbia Univ	108	3354	Mcgill Univ	94	6274
NYU	106	4158	Univ British Columbia	64	1856
Washington Univ	91	2725	Univ Sao Paulo	54	1399
Case Western Reserve Univ	82	2915	Cluster 5 (3 Items)		
Boston Univ	76	2240	Univ So Calif	109	3668
Seoul Natl Univ	75	1400	Univ S Florida	85	3173
Mt Sinai Sch Med	61	2024	Univ Miami	70	1815
Brown Univ	60	1569			

Search results from SCI-E and VoSviewer

3.3.3 Author analysis. Overall 28,580 authors have published scholarly publications related to Alzheimer disease. There are 610 authors that meet the threshold: more than 10 publications and more than 100 citations. Vellas is the author with the largest number of 112 publications in AD, with 3369 citations, 54 coming from the paper published in 2005. Cummings is the author with the highest number of 6663 citations in this field, 104 coming from a paper published in 1998, 72 from 2000 and 79 citations from an article published in 2009. Cummings Jl has 59 publications and 6663 citations. His most cited articles have been published in 1998, with 104 citations; in 2000, with 52 citations and in 2006, with 79 citations. The collaboration between the top 50 more productive authors are displayed in clusters (Table 6). Clearly Vellas (cluster 6) which have the highest number of published articles, cooperates mainly with Andrieu and Nourhashemi.

Table 6: Clusters of collaboration between authors in Alzheimer disease research, 1997-2017.

Cluster	TP	TC	Cluster	TP	TC
Cluster 1 (11 Items)			Cluster 3 (10 items)		
Soininen, H	67	3063	Lyketsos, CG	75	2870
Frisoni, GB	60	1515	Cummings, Jl	59	6663
Wahlund, LO	53	2382	Jack, Cr	47	1629
Padovani, A	38	1030	Petersen, RC	42	1858
Mecocci, P	37	1363	Weiner, Mw	38	1320
Tsolaki, M	37	1044	Lam, Lcw	37	761
Verhey, FRJ	37	1452	Thompson, Pm	37	1055
De Deyn, PP	36	1132	Rabins, PV	33	1060
Hampel, H	34	1267	Yaffe, K	33	1115
Lovestone, S	34	871	Schneider, Ls	32	1438
Panza, F	34	835			
			Cluster 4 (6 Items)		
Cluster 2 (10 Items)			Blennow, K	81	3109
Winblad, B	64	3231	Minthon, L	47	1531
Brodaty, H	55	1678	Wallin, A	46	1728
Waldemar, G	42	1464	Kurz, A	40	1210
Arai, H	39	604	Zetterberg, H	36	976
Gauthier, S	37	1326	Londos, E	33	914
Dekosky, ST	36	1480			

Fratiglioni, L	36	1367	Cluster 5 (4 Items)		
Morris, JC	35	1699	Lee, JH	49	958
Burns, A	34	978	Duara, R	37	1084
Ikeda, M	33	702	Lee, DY	36	858
			Woo, Ji	33	830
Cluster 6 (3 Items)					
Vellas, B	112	3369	Cluster 7 (3 Items)		
Andrieu, S	57	1455	Ballard, C	38	975
Nourhashemi, F	36	758	O'brien, JT	38	819
			Aarsland, D	33	782
Cluster 8 (2 Items)		1819	Cluster 9 (2 Items)		
Scheltens, P	74	920	Bennett, DA	49	2079
Van Der Flier, WM	37		Wilson, RS	33	1349

Source SCI-E and VOSviewer

3.4 Research Hotspots and Trends

3.4.1 Research Hotspots. There are 20,793 keywords identified in Alzheimer disease. Table 7 shows the top keywords with at least 200 occurrences. Except for Alzheimer, which is the search word in the study, a keywords analysis revealed that dementia, mild cognitive impairment, aging, diagnosis, risk, brain, amyloid precursor protein, depression and memory are some of the research hotspots in the study period.

Table 7: The most frequently used keywords for the study period

Keywords	Occurrences	Keywords	Occurrences
Alzheimer	7611	Cognition	408
Dementia	3852	Scale	400
Mild Cognitive Impairment	2611	Mini Mental State	386
Aging	1020	Parkinsons Disease	361
Diagnosis	990	Decline	356
Risk	938	A Beta	354
Brain	731	Apolipoprotein-E	335
Amyloid Precursor Protein	678	Cerebrospinal Fluid	329
Depression	665	Oxidative Stress	327
Memory	578	Hippocampus	318
Association	460	MRI	314

Source form SCI-E and CiteSpace

The visualization in a foam tree, through Carrot, offers an innovative non-rectangular tree map, where the size of each one represents the frequency of the topic (Fig.6). Although there are some discrepancies between the frequencies obtained with CiteSpace and Carrot, the similarity between top keywords make it a useful point of reference about the main trends (Chen et al., 2014) on AD research. The discrepancy is explained by the difference in sources working on SCI-E and PubMed.

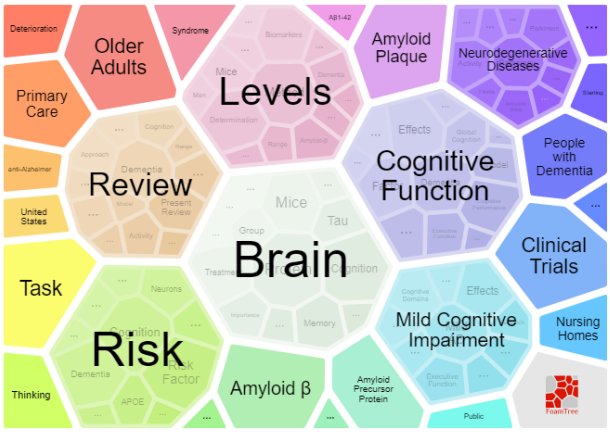


Fig.6 Major topics in Alzheimer disease. Results from PubMed extracted by Carrot.

The evolution of the keywords through time, displayed in Fig. 7, shows the relevance of Alzheimer disease, dementia and cognitive impairment as relevant topics of research.

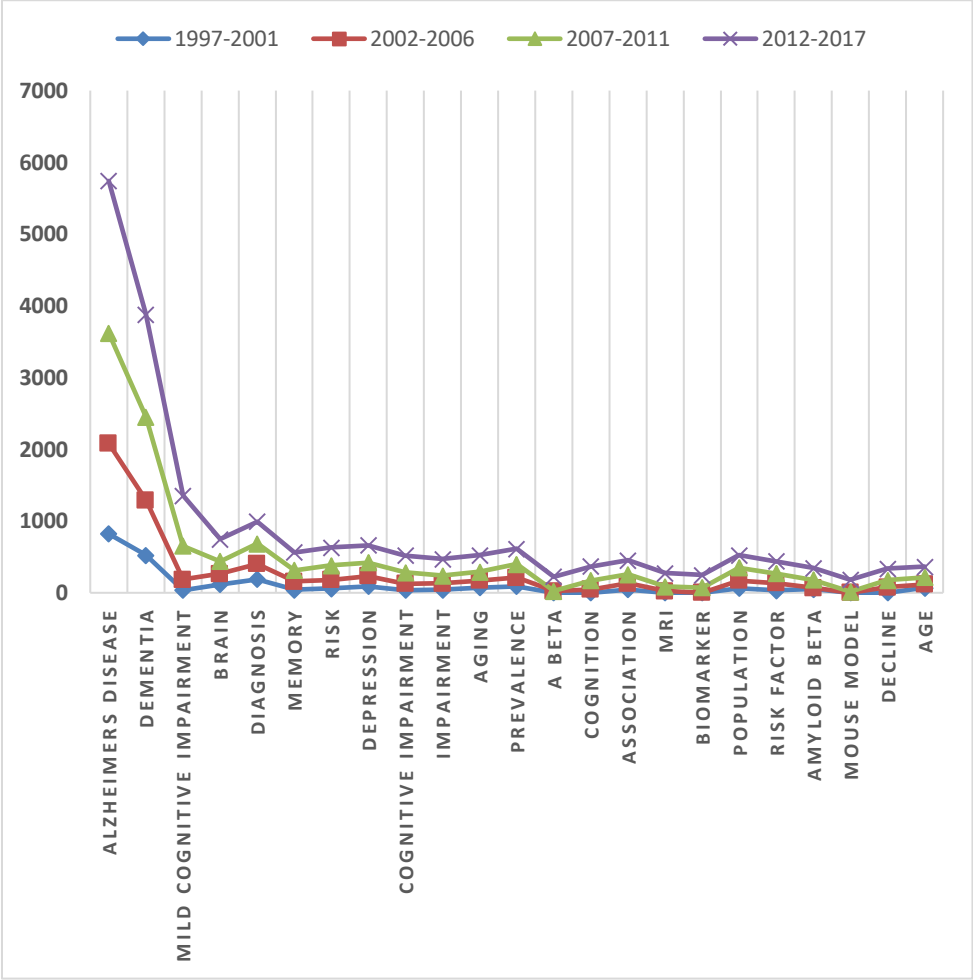


Fig.7: Visualization of the keywords of Alzheimer disease through time.

Search results from SCI-E and CiteSpace.

3.4.2 Research Trends. Burst keywords are indicators of emerging trends over time in AD, having statistically significant fluctuations on the citation count, during a short period of time (Table 8). The time interval is depicted as a blue line. The period time in which a keyword was found to have a burst is shown as a red line segment, indicating the begin year and the ending year of the duration of burst.

Prior to 2006 some burst keywords were: fronto temporal dementia, apolipoprotein E, astrocyte, vascular and senile dementia, peptide, tacrine, senile plaquemini mental state, and neurofibrillary tangle. Topics between 2007-2011 are: pshychosis, donepezil, cholinesterase inhibitor, disturbance, polymorphism, and blood pressure. Topics before 2007 are: entorhinal cortex, mci, mri, neurodegeneration, app, amyloid beta, mouse model, pathology, tau, genome wide, association, cognitive function, working memory, biomarker, diagnostic criteria and metaanalysis.

Table 8: Top keywords with strongest citation burst

Keywords	Strength	Begin	End	1997 - 2017
Senile Dementia	752.494	1997	2004	
Amyloid Beta	323.252	2013	2017	
Mouse Model	281.429	2013	2017	
Neurofibrillary Tangle	271.358	1997	2003	
Cholinesterase Inhibitor	260.735	2003	2009	
Tacrine	251.563	1998	2000	
Vascular Dementia	234.036	1998	2003	
Pathology	233.142	2013	2017	
Senile Plaque	232.168	1997	2002	
Polymorphism	227.233	2004	2009	
Synaptic Plasticity	217.852	2012	2015	
Donepezil	214.319	1999	2010	
Mri	184.525	2012	2017	
Biomarker	169.785	2015	2017	
Apolipoprotein E Genotype	145.815	2001	2006	
Genome Wide Association	140.632	2014	2016	
Blood Pressure	139.197	2005	2007	
Diagnostic Criteria	123.076	2015	2017	
Cognitive Function	122.046	2014	2016	
Entorhinal Cortex	121.757	2006	2012	
Working Memory	115.889	2014	2016	
Mci	107.401	2007	2012	
App	101.814	2012	2014	

Astrocyte	95.702	1998	2001	
Mini Mental State	95.098	1997	2003	
Rating Scale	85.877	1998	2002	
Disturbance	83.676	2002	2007	
Tau	77.436	2014	2017	
Fronto Temporal Dementia	44.462	2003	2006	
Psychosis	26.762	2000	2007	
Metaanalysis	23.849	2015	2017	
Neurodegeneration	17.515	2012	2017	
Peptide	10.129	1998	2004	

Source CSIE and CiteSpace

4. Conclusions

This study evaluates AD research during 1997-2017, through a bibliometric analysis of the patterns of documents, citations, journals, authors, countries, institutions, keywords, areas of research and trends. The 9,753 articles obtained from the science citation index expanded database (SCI-E), from Web-of-Science, were analysed. A bibliometric methodology identify the publications, citations, journals, authors, countries, institutions, keywords, areas of research and trends, during 1997–2017. This computational analysis provided the answer to various research questions stated in Section 1. There was an increasing trend of AD publications over time. The journals of "Neurobiology of Aging" and "Dementia and Geriatric Cognitive Disorders" have the largest number of publications and citations. USA has the highest number of publications and citations and its dominant position is affirmed by the number of active institutions included into the top rank. Emerging countries in the last four years in AD research are People's Republic of China, Russia, Portugal, Taiwan, Chile, Iran, Colombia, and Argentina. Velas B is the author with more publications, while Cummings JL is the author more cited. The collaboration between authors indicates a greater globalization, with complex and articulated research networks where the distance has some interesting explanation but the main factor seems to be a positive correlation with the income of the countries. These networks could also be explained by the increased number of communication technologies, which allows more international collaboration and more share of ideas and workloads.

Keyword analysis revealed the hotspots in AD studies, which were: dementia, mild cognitive impairment, aging, diagnosis, risk, brain, amyloid precursor protein, depression and memory. Burst detection identifies the trends of AD. The focus before 2006 was on anatomy, histochemistry, biochemistry, physiology and some therapeutics. Between 2007 and 2011 the

focus was directed at psychology, psychiatry, genetics, risk factors and therapeutics. After 2011 was born a different focus directed to applications of health technologies, molecular engineering, neuropsychology and applied psychology, maintaining some research in fundamental disciplines of medicine. Besides, it has appeared clinical guidelines and a new field of research interested in metaanalysis.

Bibliometric analysis has helped to characterize qualitatively and quantitatively the AD research in terms of its development, hotspots and trends of investigation, supplying the researchers with new tools in this domain. The paper helps in understanding the broad landscape of AD research and presents results useful for researchers in the area. Bibliometric analysis has helped to characterize qualitatively and quantitatively the AD research in terms of its development, hotspots, and trends of the investigation, supplying the researchers and practitioners with new tools in this domain. Our research spans 20 years of scientific literature. In order to create a representative corpus of documents for investigation, we set up the following profile in WoS: topic: "Alzheimer or Alzheimer's", indexed SCI-Expanded; timespan 1997-Nov 2017. This profile, although not exhaustive, produces a comprehensive number of documents to have been analysed. The data chosen is WoS which has the oldest and most comprehensive records of citation indexes, assumed to have a sufficient amount of high quality literature. Nevertheless, it doesn't necessarily index the totality of journals and then not all research of interest can be examined using this data (Li et al., 2010).

References

Alzheimer's Association. (2012). Alzheimer's disease facts and figures. Alzheimer's and Dementia, Vol.8, No.2, pp.131–168. doi:10.1016/j.jalz.2012.02.001.

Angel, L., Fay, S., and Isingrini, M. (2010). Electrophysiological investigation of episodic memory in aging, *Annee Psychologique*, Vol.110, No.4, pp.595-628.

Barnes DE, and Yaffe K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. Vol 9, pp. 819-828.

Barth, M., Haustein, S. and Scheidt, B. (2014). The life science in German-Chinese cooperation: an institutional-level co-publication analysis. Scientometrics, Vol.98, No.1, pp.99-117, doi: 10.1007/s11192-013-1147-9.

Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, and Johns H (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement. Vol.11, No.6, pp.718-726.

Bennett, D. A., Wilson, R. S., Schneider, J. A., and Evans, D. A., Mendes de Leon, C. F., Arnold, S. E., Barnes, L. L., and Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons, *Neurology*, 60 (12), 1909-1915. doi: 10.1212/01.WNL.0000069923.64550.9F.

Berr, C., Wancata, J., and Ritchie, K. (2005). Prevalence of dementia in elderly in Europe. *European Neuropsychopharmacology*, Vol.15, No.4, pp.463-471.

Bielak, A.A.M. (2010) How Can We Not 'Lose It' if We Still Don't Understand How to 'Use It'? Unanswered Questions about the Influence of Activity Participation on Cognitive Performance in Older Age – A Mini-Review, *Gerontology*, Vol.56, No.7, pp.507–519. doi:10.1159/000264918.

Bosch, B., Bartrés-Faz, D., Ramia, L., Arenaza-Urquijo, E.M., Fernández-Espejo, D., Carme Junqué, C., Solé-Padullés, C., Sánchez-Valle, R., Bargalló, N-, Falcónc, C. and Molinuevo, J.L. (2010). Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease, Cortex, Vol. 46, No.4, pp.451–461. doi: 10.1016/j.cortex.2009.05.006.

Chen, H., Wan, Y., Jiang, S. and Cheng, Y. (2013). Alzheimer's disease research in the future: bibliometric analysis of cholinesterase inhibitors from 1993 to 2012. Scientometrics, 98:1865-1877, doi: 10.1007/s11192-013-1132-3.

Chen, C., Dubin, R., and Kim, M. C. (2014). Emerging trends and new developments in regenerative medicine: A scientometric update (2000–2014). Expert Opinion on Biological Therapy, Vol.14, No.9, pp.1295–1317.

Chen Y, Sillaire AR, Dallongeville J, Skrobala E, Wallon D, Dubois B, Hannequin D, Pasquierthe F and Lille YOD (2017). Low Prevalence and Clinical Effect of Vascular Risk Factors in Early-Onset Alzheimer's Disease. *Journal of Alzheimers Disease, Vol.*60, No.3, pp.1045-1054. doi: 10.3233/JAD-170367.

Chuang, K. Y., Wang, M. H., and Ho, Y. S. (2013). High-impact papers published in journals listed in the field of chemical engineering. Malaysian Journal of Library and Information Science, Vol.18, No.2, pp.47–63.

Clive, B., Julian, H., Tony, H., Robin, J., and Sue, Z. (2003). Ethics and dementia: Mapping the literature by bibliometric analysis. International Journal of Geriatric Psychiatry, Vol.18, No.1, pp.41–54. doi:10.1002/gps. 770.

Cummings, J.L. (2004). Alzheimer´s Disease. *The New England Journal of Medicine*, Vol.351, pp.56-67.

Ellegaard, O. and Wallin, J.A., (2015). The bibliometric analysis pf scholarly production: How great is the impact? Scientometrics, Vol.105, No3, pp.1809-1831.

Erickson, K. I., Voss, M.W., Prakash, R.S., Bask, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., and Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory, *Proceedings of the National Academy of Sciences of the United States of America*, Vol.108, No.7, pp.3017–3022, doi:10.1073/pnas.1015950108.

Fu, H. Z., Wang, M. H., and Ho, Y. S. (2012). The most frequently cited adsorption research articles in the Science Citation Index (Expanded). Journal of Colloid and Interface Science, Vol.379, No.1, pp.148–156.

Greenwood, C. E. and Parrott, M. D. (2017). Nutrition as a component of dementia risk reduction strategies. Healthcare Management Forum 2017, Vol.30, No.1, pp. 40-45.

Hilal S,Akoudad S,van Duijn CM, Niessen WJ,Verbeek MM,Vanderstichele H,Stoops E,Ikram MA,and Vernooij MW (2017). Plasma Amyloid-β Levels, Cerebral Small Vessel Disease, and Cognition: The Rotterdam Study. Journal of Alzheimers Disease. 2017; Vol.60, No.3, pp.977-987. doi: 10.3233/JAD-170458.

Jalbert, J.J., Daiello, L.A., and Lapane, K. (2008). Dementia of the Alzheimer Type. Epidemiologic Review, Vol.30, pp.15-34.

Li, L. L., Ding, G. H., Feng, N., Wang, M. H., and Ho, Y. S. (2009). Global stem cell research trend: Bibliometric analysis as a tool for mapping of trends from 1991 to 2006. Scientometrics, Vol.80, No.1, pp.39–58. doi:10.1007/s11192-008-1939-5.

Li, J., Burnham, J.F., Lemley, T., and Britton, R.M (2010). Citation analysis; Comparison of Web of Science, Scopus, SciFinder, and Google Scholar. Journal of electronic resources in medical libraries, Vol.7, No.3, pp.196-217, doi: 10.1080/15424065.2010.505518.

Mahapatra, M. (1985), On the validity of the theory of exponential growth of scientific literature, In *Proceedings of the 15th IASLIC conference, December*, pp. 61–70.

Mao, N., Wang, M. H., and Ho, Y. S. (2010). A bibliometric study of the trend in articles related to risk assessment published in science citation index. Human and Ecological Risk Assessment, Vol.16, No 4, pp.801–824. doi:10.1080/10807039.2010.501248.

Metaxas A,Vaitheeswaran R,Jensen KT,Thygesen C,Ilkjaer L,Darvesh S,and Finsen B (2017). Reduced Serotonin Transporter Levels and Inflammation in the Midbrain Raphe of 12-month-old APPswe/PSEN1dE9 Mice. *Current Alzheimer Research*. doi: 10.2174/1567205014666171004113537.

Norton S., Matthews F.E., Barnes D.E., Yaffe K., and Brayne C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol.Vol.13, No.8, pp.788-794.

Prince M, Wimo A, Guerchet M, Ali GC, and Wu YT (2015), Prina M. World Alzheimer Report. The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost and Trends. London, England: Alzheimer's Disease International.

Sakai, S., Yoshida, H., Hirai, Y., Asari, M., Takigami, H., Takahashi, S., et al. (2011). International comparative study of 3R and waste management policy developments. Journal of Material Cycles and Waste Management, Vol.13, No. 2, pp.86–102. doi:10.1007/s10163-011-0009-x.

Sorensen, A. A. (2009). Alzheimer's disease research: Scientific productivity and impact of the top 100 investigators in the field. Journal of Alzheimer's Disease, Vol.16, No.3, pp. 451–465. doi:10.3233/JAD-2009-1046.

Stern, Y., Albert, S., Tang, M.-X., and Tsai, W.Y. (1999). Rate of memory decline in AD is related to education and occupation. Cognitive reserve? *Neurology,* Vol.53, No.9, pp.1942. doi: 10.1212/WNL.53.9.1942.

Valenzuela, M. and Sachdev, P. (2006). Brain reserve and dementia: a systematic review, *Psychological Medicine,* Vol.36, No.4, pp. 441-454, doi: 10.1017/S0033291705006264.

Wang, L. H., Wang, Q. H., Zhang, X., Cai, W. W., and Sun, X. H. (2013). A bibliometric analysis of anaerobic digestion for methane research during the period 1994–2011. Journal of Material Cycles and Waste Management, Vol.15, No.1, pp.1–8. doi:10.1007/s10163-012-0094-5.

Wen, H., and Huang, Y. (2012). Trends and performance of oxidative stress research from 1991 to 2010. Scientometrics, Vol.91, No.1, pp. 51–63. doi:10.1007/s11192-011-0535-2.

Zhou, X., and Zhao, G. (2015). Global liposome research in the period of 1995-2014: a bibliometric analysis. Scientometrics, Vol.105, pp.231-248, doi: 10.1007/s11192-015-1659-6.

Ziegler-Graham K., Brookmeyer, R., Johnson, E., and Arrighi, H.M. (2008). Worldwide variation in the doubling time of Alzheimer's disease incidence rates. Alzheimers Dement., Vol.4, No.3, pp.16-23, http://dx.doi.org/10.1016/j.jalz.2008.05.2479.

Zilka, N., and Novak M. (2006). The tangled story of Alois Alzheimer, Vol.107, No. 9-10, pp.343-5.

. **Final Refereeing Decision IJMDA_202430**

Caixa de entrada x

IJMDA-Luiz favero x

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Dear Maria Helena Pestana, Margarida Lemos Sobral,

Ref: Submission "Alzheimer´s Disease Research: A Network Science Approach"

Congratulations, your above mentioned submitted article has been refereed and accepted for publication in the International Journal of Multivariate Data Analysis. The acceptance of your article for publication in the journal reflects the high status of your work by your fellow professionals in the field.

Your continuing help and cooperation is most appreciated.

Best regards,

Prof. Luiz Paulo Fávero

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