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REVIEW
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Neurodegenerative Diseases and Cholesterol: Seeing the Field Through the Players

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Neurodegenerative diseases, namely Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD) together with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), devastate millions of lives per year worldwide and impose an increasing socio-economic burden across nations. Consequently, these diseases occupy a considerable portion of biomedical research aiming to understand mechanisms of neurodegeneration and to develop efficient treatments. A potential culprit is cholesterol serving as an essential component of cellular membranes, as a cofactor of signaling pathways, and as a precursor for oxysterols and hormones. This article uncovers the workforce studying research on neurodegeneration and cholesterol using the TeamTree analysis. This new bibliometric approach reveals the history and dynamics of the teams and exposes key players based on citation-independent metrics. The team-centered view reveals the players on an important field of biomedical research.

Keywords: neurologic disease, bibliometric analyses, scientific impact, sterol, research evaluation, informetric, scientometric, key opinion leader

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INTRODUCTION

Neurodegenerative disorders devastate millions of lives worldwide and impose an increasing socio-economic burden (Kalia and Lang, 2015; Feigin et al., 2017; Erkkinen et al., 2018; El-Hayek et al., 2019). Research within the last decades has helped to clarify the mechanisms underlying each disease and suggested new therapeutic approaches (Fu et al., 2018; Ga et al., 2018; Jucker and Walker, 2018; Reich et al., 2018; Lassmann, 2019; Savelieff et al., 2019; Schwartz et al., 2021). A decisive step is the identification of molecular culprits that provoke or contribute to the dysfunction and degeneration of neurons. In the case of AD, research focused on three targets: hyperphosphorylated forms of tau protein, proteolytic fragments of amyloid precursor protein, and specific variants of apolipoprotein E (Long and Holtzman, 2019). A prime target for PD-related research has been alpha synuclein (Rocha et al., 2018), but other genes, as well as environmental factors, have come under scrutiny (Deng et al., 2018; Bandres-Ciga et al., 2020; Blauwendraat et al., 2020). In the case of amyotrophic lateral sclerosis (ALS), superoxide dismutase 1 has been investigated intensely as it was the first gene shown to be mutated in familial forms of the disease (Rosen et al., 1993).

TABLE 1 | Query terms used for the literature search in PubMed/MEDLINE.

Query term*	Article count
(Q1 AND Q2) NOT Q3	4,775
(Alzheimer*[tiab]) AND Q2) NOT Q3	2,514
(Multiple sclerosis[tiab] AND Q2) NOT Q3	570
(Parkinson*[tiab] AND Q2) NOT Q3	459
((Lou Gehrig* disease[tiab] OR amyotrophic lateral sclerosis[tiab]) AND Q2) NOT Q3	132
(Huntington*[tiab] AND Q2) NOT Q3	116

Query term 1 (Q1): ((Pick's disease[tiab] OR progressive supranuclear palsy[tiab] OR tauopathy[tiab] OR tauopathies[tiab] OR neuronal ceroid lipofuscinosis[tiab] OR hereditary spastic paraplegia[tiab] OR ataxia telangiectasia[tiab] OR creutzfeldt-jacob[tiab] OR prion disease[tiab] OR frontotemporal dementia[tiab] OR fronto-temporal dementia[tiab] OR polyglutamine disease[tiab] OR spinocerebellar ataxia[tiab] OR spino-cerebellar ataxia*[tiab] OR motor neurone disease[tiab] OR motor neuron disease[tiab] OR motoneuron disease[tiab] OR Lou Gehrig* disease[tiab] OR amyotrophic lateral sclerosis[tiab] OR huntington*[tiab] OR parkinson*[tiab] OR alzheimer*[tiab] OR neurodegenerative[tiab] OR neurodegeneration[tiab] OR spinal muscular atrophy[tiab] OR multiple system atrophy[tiab] OR multiple sclerosis[tiab] OR dementia[tiab]). Query term 2 (Q2): (sterol OR cholesterol OR hydroxycholesterol OR hydroxy-cholesterol OR oxysterol). Query term 3 (Q3): (review[pt] OR niemann-pick disease type c2[tiab] OR niemann-pick type c2[tiab] OR niemann-pick disease type c1[tiab] OR niemann-pick type c1[tiab] OR niemann-pick type c[tiab] OR niemann-pick disease type c[tiab]).

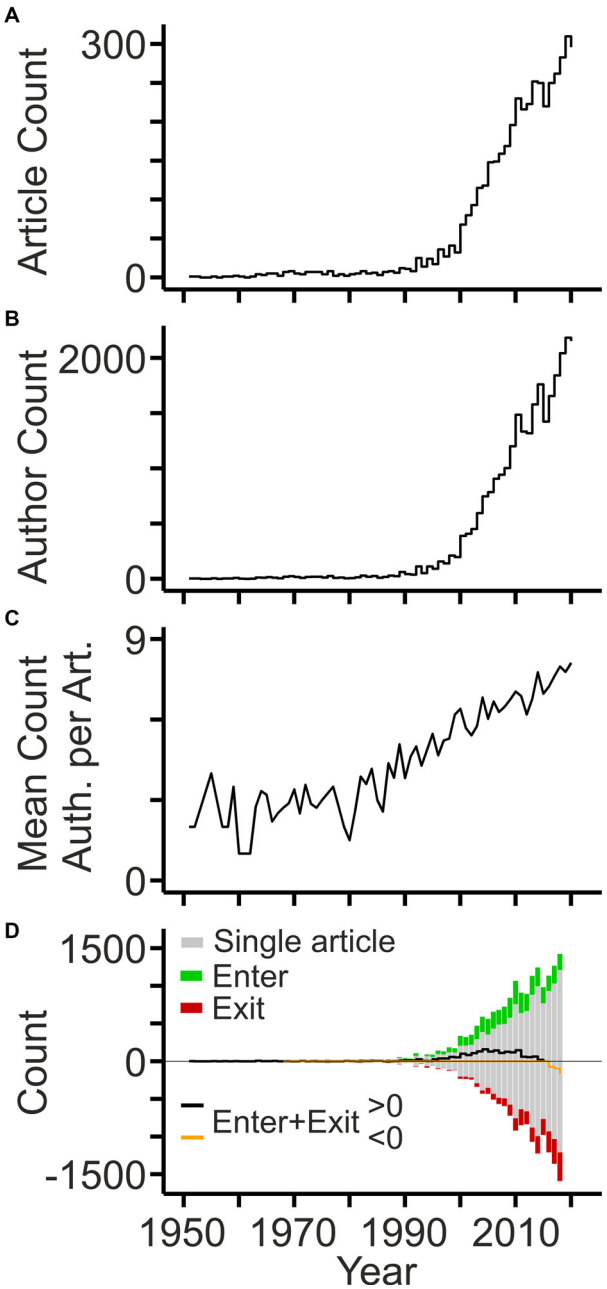

FIGURE 1 | Development of the workforce. **(A)** Annual counts of original articles related to cholesterol and neurodegeneration (PubMed query shown in **Table 1**). **(B)** Annual counts of authors contributing to the field per year. **(C)** Mean number of authors listed on article bylines per year. **(D)** Annual counts of authors entering (green bars) and exiting (red bars) the field per year based on the first and last year of publication, respectively. Black and orange lines indicate the sum of annual author counts. Gray bars indicate the number of authors contributing single articles to the field (shown as negative and positive values).

TAR DNA binding protein-43 (TDP-43) has become a target for ALS- and frontotemporal dementia-related research, as it was identified as a major component of ubiquitin-positive inclusions (Neumann et al., 2006). Since then, other genes have come under study as disease-causing alleles were identified in familial forms of ALS (Chia et al., 2018; Mejzini et al., 2019). Huntingtin has been at the center of attention as the long-sought gene bearing Huntington's disease (HD)-causing mutations (The Huntington's Disease Collaborative Research Group, 1993). Repeat expansions similar to those induced by the Huntingtin alleles cause neurodegeneration in numerous diseases including ALS and frontotemporal dementia by combinations of distinct molecular mechanisms (Malik et al., 2021; Schwartz et al., 2021). Research on multiple sclerosis (MS) has focused on immune and glial cells since chronic inflammation and demyelination are known pathologic changes preceding neurodegeneration (Faissner et al., 2019; Lassmann, 2019; Voet et al., 2019).

Why should cholesterol play a role in these diseases? Cholesterol is one of the most widely known and most studied biological molecules due to its involvement in cardiovascular and other diseases (Goldstein and Brown, 2015; Tall and Yvan-Charvet, 2015; Gliozzi et al., 2021) and due to its functions as a component of membranes in eukaryotic cells (Yeagle, 1985), as a cofactor of signaling pathways and as a precursor for steroid hormones (Miller and Auchus, 2011; Prabhu et al., 2016). Notably, cholesterol is also converted to biologically active oxysterols by specific enzymes or by autoxidation (Mutemberezi et al., 2016; Wang et al., 2021). Given the diverse functions of cholesterol, its cellular homeostasis relies on a multitude of proteins and mechanisms (Ikonen, 2008; Luo et al., 2020). In the brain, cholesterol represents a major building block due to the diversity and sheer mass of membraneous structures. This includes highly branched axons and dendrites of neurons (Elston and Fujita, 2014), fine perisynaptic processes of astrocytes (Oberheim et al., 2009), countless synaptic vesicles (Binotti et al., 2021), and the multi-layered myelin sheaths surrounding axons (Schmitt et al., 2015). Based on these considerations, disturbances of cholesterol homeostasis seem likely to cause neuronal dysfunction and

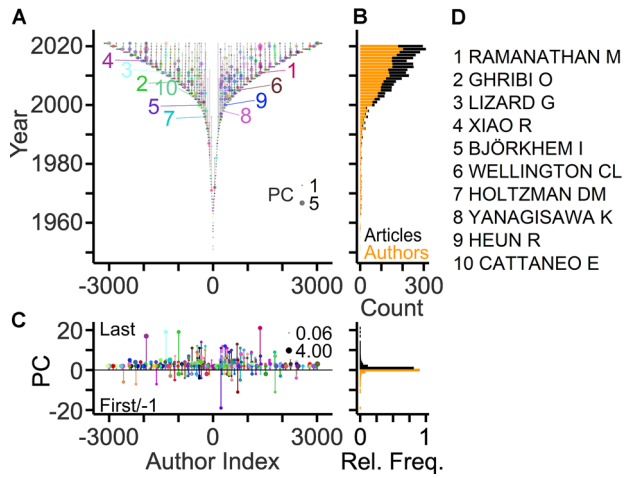

FIGURE 2 | Publication records of last authors. **(A)** TeamTree graph showing the publication records of the last authors contributing to the field. Circles connected by vertical gray lines represent for each author the years of publications as the last author plotted against a chronologic author index with alternating signs and author-specific colors to enhance visibility. Circle area indicates publication count (PC) per year. Numbers indicate authors with 10 largest PCs (names indicated in panel **D**). **(B)** Number of authors entering the field per year (orange) and of articles (black) published per year. **(C)** Left, PCs per author indicating last and first author articles by positive and negative values, respectively. Circle area indicates the average number of publications per year. Right, relative frequency distributions of PC values shown on the left. **(D)** Names of authors with largest PCs in the field.

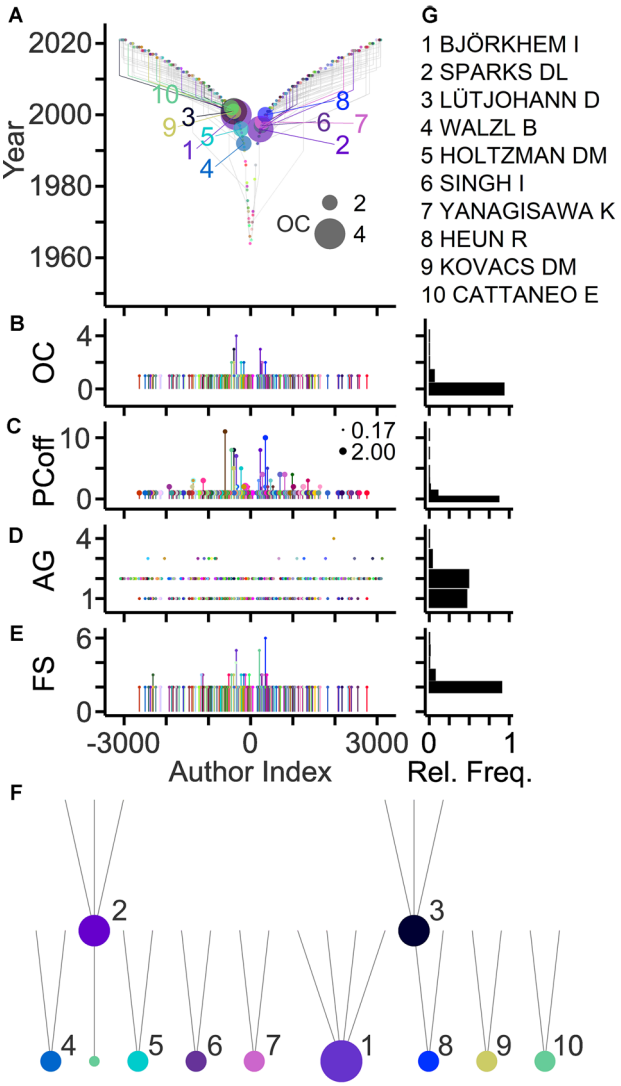

FIGURE 3 | Genealogic relations in the field. **(A)** TeamTree graph showing genealogic relations among authors. Circles and gray lines indicate ancestor-offspring connections based on first author-last author pairs on article bylines. Connections of authors with the 10 largest offspring count (OC) values are shown in color (names indicated in panel **G**). Circle area indicates OC value. The signs of author indices of offspring and of ancestors were adjusted to the first-generation ancestor. **(B–E)** Quantitative data showing for individual last authors, the number of offspring **(B)** the number of articles published together with offspring (PCoff; circle area indicates average PC per year) **(C)**, the generation of authors (AG) starting with AG = 1 for first ancestors **(D)** and the family size (FS) of individual first-generation ancestors comprising all offspring across subsequent generations **(E)**. **(F,G)** Family trees **(F)** and names **(G)** of authors with 10 largest OC values (indicated by circle area).

degeneration. The mechanisms of cholesterol homeostasis in brain cells are probably distinct from those operating in the rest of the body (Dietschy, 2009; Pfrieger and Ungerer, 2011; Zhang and Liu, 2015; Mahley, 2016; Moutinho et al., 2016; Yoon et al., 2016; Hussain et al., 2019). Possible implications of cholesterol and derived molecules in neurodegenerative diseases have been reviewed elsewhere (Martín et al., 2014; Zarrouk et al., 2014; Leoni and Caccia, 2015; Doria et al., 2016; Arenas et al., 2017; Chang et al., 2017; Testa et al., 2018; Zarrouk et al., 2018; Adorni et al., 2019; Griffiths and Wang, 2019; Hussain et al., 2019; Jeong et al., 2019; Jin et al., 2019; Loera-Valencia et al., 2019; Petrov and Pikuleva, 2019; Segatto et al., 2019; Blauwendraat et al., 2020; González-Guevara et al., 2020; McFarlane and Kędziora-Kornatowska, 2020; Sáiz-Vazquez et al., 2020; Dai et al., 2021; Duong et al., 2021; Feringa and van der Kant, 2021; García-Sanz et al., 2021; Pikuleva and Cartier, 2021; Samant and Gupta, 2021). This article shows the workforce driving research in the field using original research articles obtained from MEDLINE (**Table 1**) and a new bibliometric approach (Pfrieger, 2021; https://github.com/fw-pfrieger/TeamTree). Bibliometric analyses of other aspects can be found elsewhere (Guido et al., 2015; Barboza and Ghisi, 2018; Zhang et al., 2020; Du et al., 2021; Li et al., 2021; Rizzi et al., 2021). Articles related to Niemann-Pick type C disease were excluded from the analysis as this rare lysosomal storage disorder is directly linked to perturbed cholesterol transport (Loftus et al., 1997; Naureckiene et al., 2000; Vanier, 2010).

DEVELOPMENT OF THE WORKFORCE CONTRIBUTING TO THE FIELD

The earliest publications date back to the 1950s when three groups investigated the cholesterol content in tissues and body fluids of patients with dementia (Mori and Barucci, 1951;

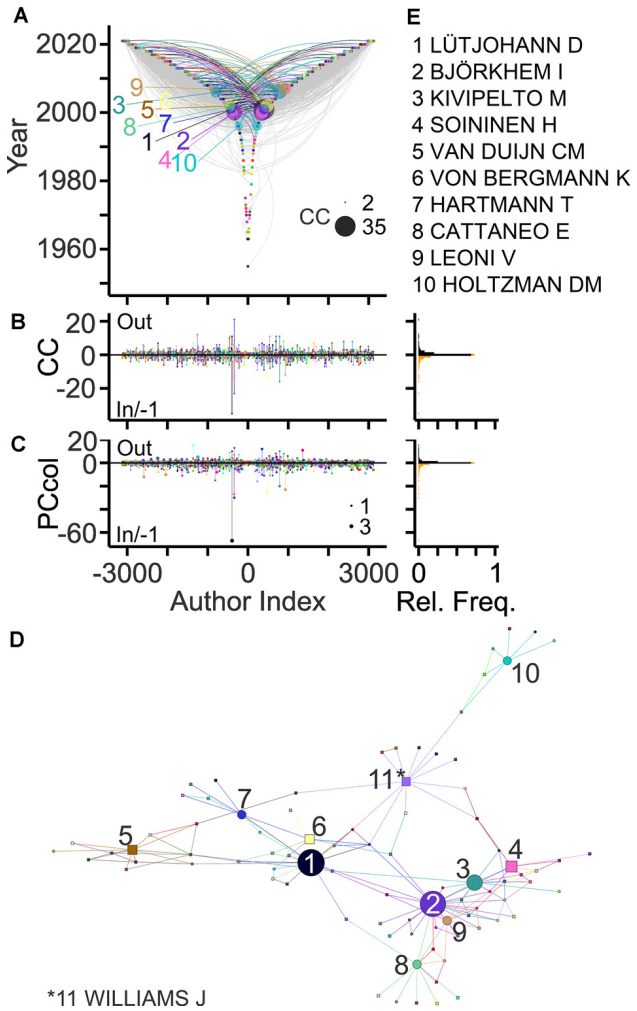

FIGURE 4 | Collaborative connections in the field. **(A)** TeamTree graph showing collaborations between last authors (out; negative author index) and (non-first) co-authors (in; positive author index) on article bylines. For out- and in-degree connections an author lists other authors as co-authors and an author is listed as a co-author, respectively. Connections of authors with 10 highest connection count (CC) values (in+out) are shown in color (names indicated in panel **E**). Circle areas indicate CCout and CCin values of these authors. **(B,C)** Left, counts of collaborators **(B)** and of collaborative articles **(C)** per author. Circle area indicates PCannu. Right, relative frequency distributions of parameters shown on the left. **(D,E)** Network **(D)** and names **(E)** of authors with 10 largest CC values. Symbol areas **(D)** indicate CC values normalized to the maximum. Circles and rectangles represent family and non-family authors, respectively.

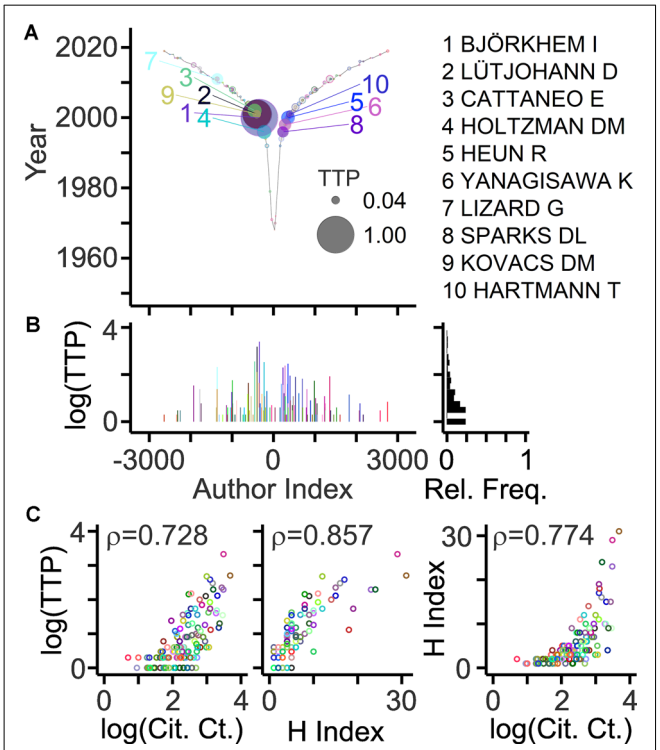

FIGURE 5 | Author ranking based on the TeamTree product. **(A)** Graph showing the TeamTree product (TTP) of individual last authors in the field represented by their author indices. This new metric takes into account publication records, offspring training and mentorship, and collaborative connections. Numerically, it represents the product of PC (last author articles) × OC × CC. Circle sizes indicate TTP values normalized to the maximum. Colored circles and numbers indicate authors with 10 highest values. Their names are shown on the right. Gray circles with colored border indicate authors with TTP values above zero. **(B)** Log10(TTP) values and their relative frequency distribution. **(C)** Scatterplots with circles representing individual authors (indicated by color; different from panels **A,B**) with their TTP values (log10) plotted against the total number of citing articles (left; Cit. Ct.; log10 values) and their H indices (middle) and with their H indices plotted against the total number of citing articles (right; log10 values). Numbers represent correlation coefficients [Spearman's rho values; two-sided test; $n = 126$; $S = 90{,}803$ (left)/47,558 (middle)/75,414 (right); $p < 10^{-10}$]. Citation-related parameters were calculated from bibliographic records obtained by a Web of Science query (Clarivate Analytics).

Scanu et al., 1955) and MS (Chiavacci and Sperry, 1952; Poser and Curran, 1958). The number of articles published per year remained relatively low until the 1990s and increased thereafter. Since 2000, the annual count of articles has grown linearly reaching around 300 articles per year in 2020 (**Figure 1A**). The number of authors listed on the article byline grew in parallel, however at a much stronger pace reaching more than 2,000 per year within the last years (**Figure 1B**). The strong expansion of the workforce was due to an increasing number of authors per article (**Figure 1C**). Notably, the expansion of the field was mainly driven by authors contributing single articles, as their number grew steadily. The balance of authors publishing in the field for more than 1 year has become negative within the last years, but the number of authors leaving the field within the last years is inherently inaccurate (**Figure 1D**).

PUBLICATION RECORDS, FAMILY RELATIONS, AND COLLABORATIVE CONNECTIONS IN THE FIELD

More information about the workforce can be drawn by analyzing the authors on specific positions of the article byline, which indicate the roles and contributions of authors (Claxton, 2005; Marušić et al., 2011). A total of ∼3,100 authors was listed on the last byline position of articles identifying these

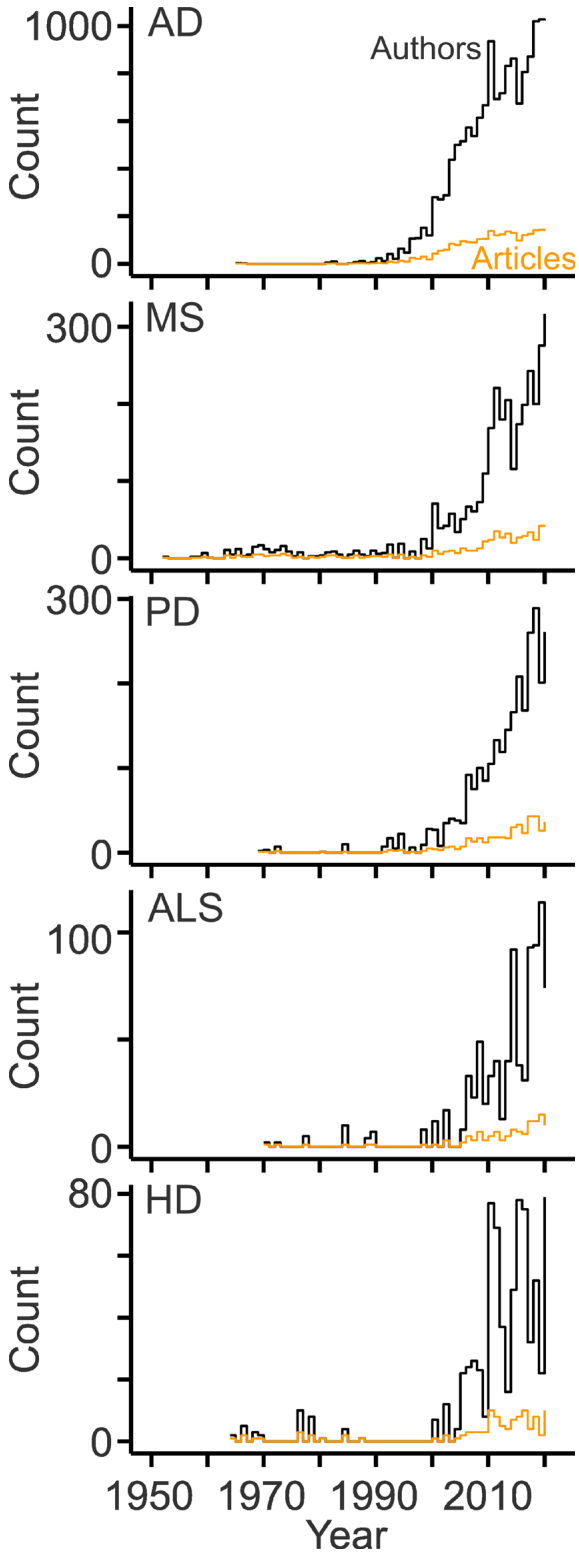

FIGURE 6 | Development of the disease-specific workforce. Line plots showing counts of original articles (orange) and of the contributing authors (black) per year related to cholesterol and the indicated diseases. AD, Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease.

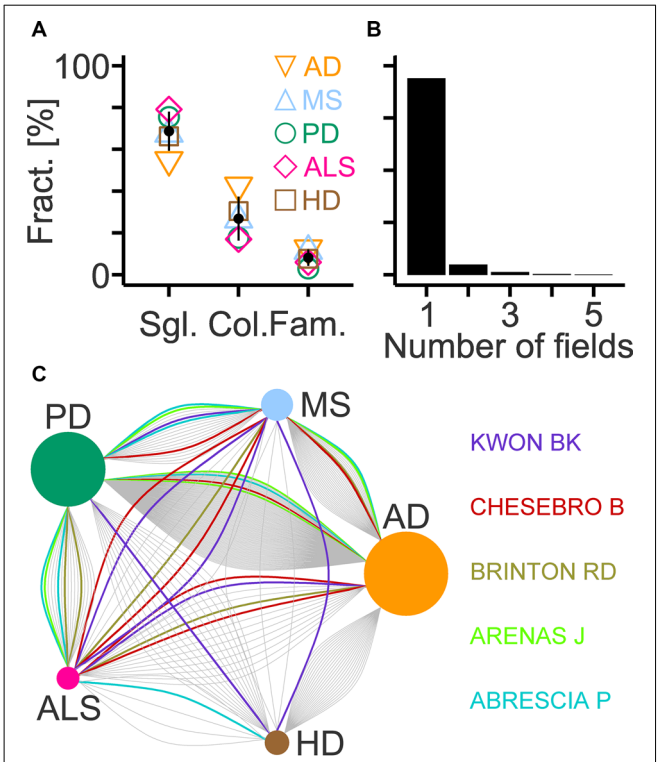

FIGURE 7 | Workforce composition and overlap across selected diseases. **(A)** Fractions of authors contributing single articles compared to the total workforce (Sgl.), of collaborating authors among last authors (Col.) and of authors with family ties among last authors (Fam.) in indicated fields (AD, Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease). Black circles and lines indicate mean and standard deviation (n = 5), respectively. **(B)** Histogram showing the fraction of last authors that contributed articles to the indicated number of fields. **(C)** Diagram showing connections between two diseases that are established by last authors contributing to both fields. Names and colored lines indicate the last authors with the highest number of connections (n = 6). Circle size represents the number of connections normalized to the maximum (AD; 160 links).

authors as principal investigators in the field. This corresponds to 10% of the total workforce. The development of the field with respect to these contributors is shown in **Figure 2A** using TeamTree graphs. In this type of scatterplot, the years of publication are plotted against a chronologic index assigned to each author (Pfrieger, 2021). The number of last authors entering the field per year has grown steadily during the last two decades (**Figure 2B**). The total publication counts of individual last authors reached up to 21 articles, but the large majority (81%) contributed single articles (**Figure 2C**) as observed for the entire workforce (**Figure 1D**). Ranking authors by PCs identified the top contributors among the last authors (**Figure 2D**).

Genealogical relations in a field can be derived from the last and first authors on article bylines representing ancestor and offspring, respectively (Pfrieger, 2021). **Figure 3A** shows family relations among authors highlighting those with the largest offspring counts. About 10% of last authors published previously as first authors thus qualifying as offspring, and 7% of last authors

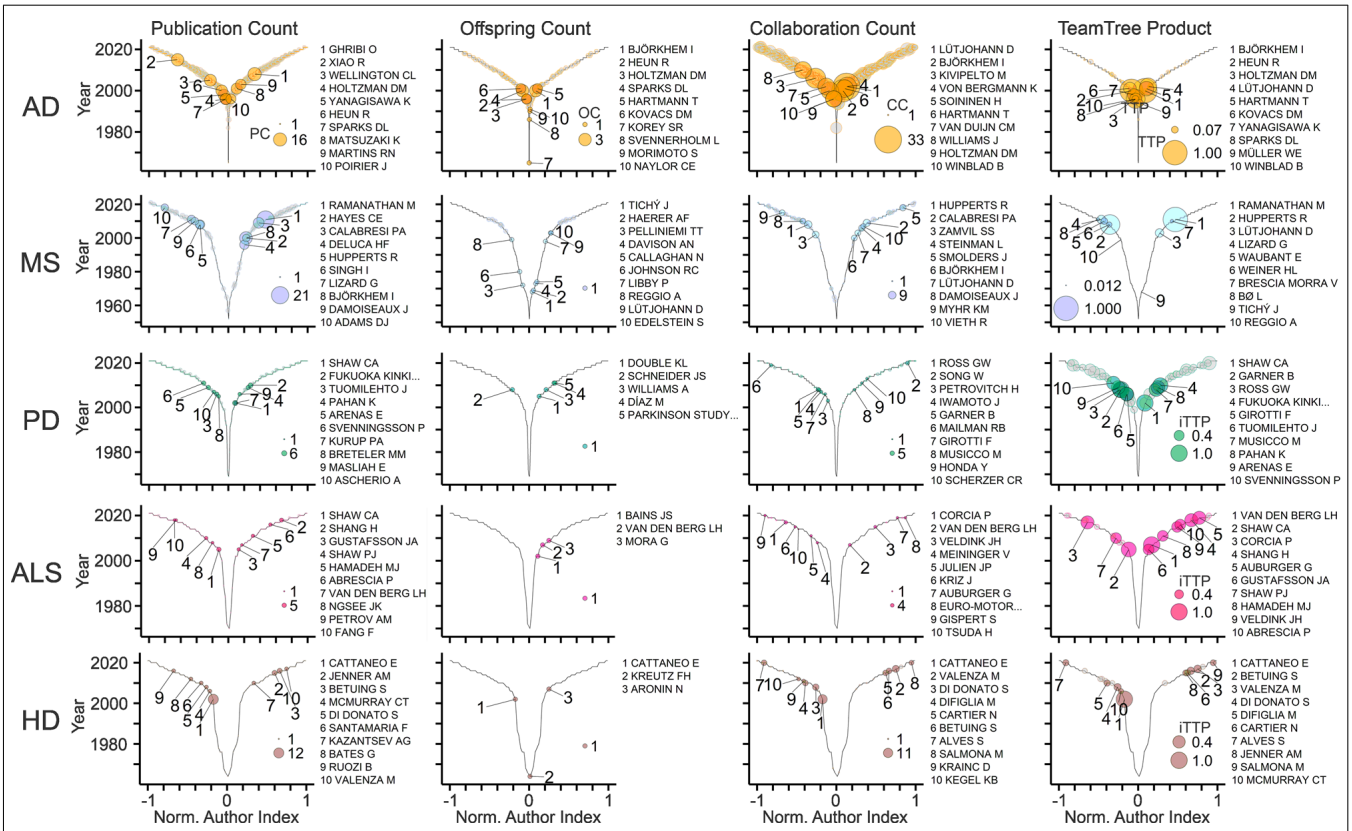

FIGURE 8 | In-depth view on the field-specific workforce. TeamTree graphs showing counts of publications (PC), offspring (OC), collaborative connections (CC), and the TeamTree product (TTP) in the indicated fields (AD, Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease) together with names of authors with the 10 largest values for each parameter. Note that for PD, ALS and HD, TTP values were replaced by an inclusive version of this measure (iTTP). For iTTP, zero counts of OC or CC values are set to one to include authors without offspring or lacking collaborators in the TTP-based ranking.

qualified as ancestors (**Figure 3B**). These ancestors generated up to four offspring authors and published up to 10 articles with their offspring (**Figure 3C**). Overall, the field comprised 192 families with up to six members spanning maximally four generations (**Figures 3D,E**). The large majority of families (91%) had only two members. Ranking by OCs revealed the most prolific authors and their families in the field (**Figures 3F,G**).

Collaborative connections can be delineated based on middle and last byline positions (Newman, 2001; Pfrieger, 2021). **Figure 4** exposes collaborations between authors contributing to the field. In total, 43% of the authors established collaborations with maximally 46 other authors and published up to 77 collaborative articles as last and co-author, respectively (**Figures 4B,C**). Ranking authors based on collaboration counts revealed the most strongly connected teams in the field and their networks (**Figures 4D,E**).

IDENTIFICATION OF MAJOR CONTRIBUTORS TO THE FIELD

An important goal of bibliometric analyses is to estimate the contribution of individual authors. The "key players" may serve as experts, key opinion leaders, referees, and collaborators. Different indicators of scientific production have been explored including PCs, citations, invitations, grants, and honors (Hicks et al., 2015; Schimanski and Alperin, 2018; Braithwaite et al., 2019). Original articles represent an accessible primary basis to estimate the contribution of an author. A new approach takes into account publication record, offspring generation, and collaborative connections, and delivers a new citation-independent parameter named TeamTree product (TTP; Pfrieger, 2021). Based on this parameter, key players studying neurodegenerative diseases and cholesterol are exposed in **Figure 5**. Due to the high selectivity, only a small fraction of authors (5%) reached TTP values above zero. Notably, TTP values of authors were strongly correlated with citation-dependent measures such as the total number of citations or the H index (**Figure 5C**).

DISEASE-SPECIFIC WORKFORCE ANALYSES

To gain deeper insight, diseases with the largest numbers of publications were analyzed separately (**Table 1**). Notably, AD-related research produced half of the articles published in

the field (**Table 1**). Overall, the fields showed marked differences with respect to length and growth pattern: MS has the longest and most continuous publication record (**Figure 6**). Except for two articles published in the 1960s, research on AD and cholesterol started in the 1980s. The subsequent growth of this field was probably triggered by discoveries that the epsilon allele of apolipoprotein E (Corder et al., 1993; Poirier et al., 1993; Rebeck et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993) and high blood levels of cholesterol raise the risk of sporadic AD (Kivipelto et al., 2001). Parallel studies revealed connections between cholesterol and beta amyloid (Hartmann et al., 1994; Bodovitz and Klein, 1996; Avdulov et al., 1997; Howland et al., 1998; Simons et al., 1998; Refolo et al., 2000; Fassbender et al., 2001; Kojro et al., 2001; Puglielli et al., 2001; Runz et al., 2002; Wahrle et al., 2002) and between statins and AD (Wolozin et al., 2000; Refolo et al., 2001). The other disease fields are characterized by intermittent publication activity starting in the 1960s (HD) and 1970 (PD, ALS) and a more continuous development since 2000 (**Figure 6**). In the case of HD, pioneering studies showing links to cholesterol synthesis were published at the beginning of the 2000s (Sipione et al., 2002; Valenza et al., 2005). In all fields, the workforce grew more strongly than the number of publications (**Figure 6**) due to the increasing number of authors per article (**Figure 1C**). The ratios of author counts to publication counts were very similar across fields (6.6 ± 0.5; mean $\pm$ standard deviation; $n = 5$).

In each field, most authors contributed single articles with their fractions ranging from the lowest value in AD to the highest in ALS (**Figure 7A**). Inversely, the AD and ALS fields showed the highest and lowest fraction of authors involved in collaborations, respectively (**Figure 7A**). Authors with family ties represented a minority of the workforce with disease-specific fractions between 3% and 13% (**Figure 7A**). The analysis also revealed relatively little overlap among the workforce of each disease. Only 6% of authors (146 out of 2,379) contributed articles to more than one field (**Figure 7B**) and established up to six connections among them with AD and PD showing the largest workforce overlap (**Figure 7C**).

TeamTree graphs illustrate the workforce that studies links between cholesterol and the selected diseases (**Table 1**; **Figure 8**). Not surprisingly key players of the AD field dominate the global rankings (**Figures 2–5**, **8**). The analysis shows further that OCs are particularly sensitive to the size of the field. In those with the lowest number of articles and the smallest workforce (PD, ALS, HD), authors produced maximally one offspring indicating that this parameter requires a critical mass of authors (**Figure 8**). The TTP values reveal distinct disease-specific origins of the top 10 contributors. Notably, in the AD field, these authors entered the field within one decade starting in the 1990s, whereas, in other fields, these contributors entered after the year 2000 (**Figure 8**).

CONCLUSIONS

The new bibliometric analysis provides a detailed view of the development and structure of the workforce driving research on cholesterol and neurodegenerative diseases and complements content-specific summaries. The analysis revealed that the field started in the 1950s and remained relatively small until the 1990s. Except for MS, all fields showed intermittent publications, but a strong growth since 2000. The continuous expansion of the workforce during this period was mainly driven by authors contributing single articles although their contribution varied among the diseases analyzed. More than half of the articles are related to AD, therefore, the family ties, collaborative connections, and key players of this field dominate the overall picture. The analysis has caveats. A key challenge for this and other bibliometric approaches are ambiguous author names, as distinct authors can share the same name precluding correct evaluation (Smalheiser and Torvik, 2009). Evaluation of contributions based on single metrics such as TTP values is context-dependent, unsuited to evaluate junior scientists, and insensitive to ground-breaking contributions from small teams or from teams that contribute only briefly to a field.

AUTHOR CONTRIBUTIONS

FWP designed the review, performed literature queries, wrote and validated the code, analyzed the bibliographic records, prepared figures, and wrote the manuscript.

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