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ORIGINAL ARTICLE

A strategic neurological research agenda for Europe: Towards clinically relevant and patient-centred neurological research priorities

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Abstract

Background and purpose: Neurological disorders constitute a significant portion of the global disease burden, affecting >30% of the world's population. This prevalence poses a substantial threat to global health in the foreseeable future. A lack of awareness regarding this high burden of neurological diseases has led to their underrecognition, underappreciation, and insufficient funding. Establishing a strategic and comprehensive research agenda for brain-related studies is a crucial step towards aligning research objectives among all pertinent stakeholders and fostering greater societal awareness.

Methods: A scoping literature review was undertaken by a working group from the European Academy of Neurology (EAN) to identify any existing research agendas relevant to neurology. Additionally, a specialized survey was conducted among all EAN

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scientific panels, including neurologists and patients, inquiring about their perspectives on the current research priorities and gaps in neurology.

Results: The review revealed the absence of a unified, overarching brain research agenda. Existing research agendas predominantly focus on specialized topics within neurology, resulting in an imbalance in the number of agendas across subspecialties. The survey indicated a prioritization of neurological disorders and research gaps.

Conclusions: Building upon the findings from the review and survey, key components for a strategic and comprehensive neurological research agenda in Europe were delineated. This research agenda serves as a valuable prioritization tool for neuroscientific researchers, as well as for clinicians, donors, and funding agencies in the field of neurology. It offers essential guidance for creating a roadmap for research and clinical advancement, ultimately leading to heightened awareness and reduced burden of neurological disorders.

KEYWORDS
Europe, neurological disorders, research agenda, research gaps, research priorities

INTRODUCTION

Neurological disorders contribute massively and increasingly to the global burden of disease, with at least one in three people worldwide being diagnosed with a neurological disease, and this burden is increasing following the COVID-19 pandemic [1]. The impact of neurological disorders on patients is staggering also in terms of years lost in disability (showing an increase of 15% in the past 30 years), premature death (increasing 39% in past 30 years) and high levels of stigma and discrimination [2]. Moreover, the costs of neurological disorders to health care systems and society are immense. In 2012, the total cost of disorders of the brain in Europe was estimated at €798 billion (equivalent to €1.037 billion in 2023), including direct costs (37% direct health care costs and 23% direct nonmedical costs) and indirect costs associated with production losses (40%) [3]. This equals the sum of the costs of all cardiovascular and oncological diseases taken together [4]. The level of awareness of this high burden of neurological diseases is still insufficient among health care professionals, academics, researchers, politicians, civil servants (in particular, ministries of health), industry, and the general public, which results in neurological care, neurological education, and the need for brain research being greatly undervalued and underfunded. Whereas the burden of neurological disorders is >30% of all disorders, the estimated funding level for neurological research is only 10% of the overall funding [5]. As a fundamental outcome of different national, international, and global awareness campaigns, neurological disorders have been identified as a global health imperative in a resolution of the World Health Assembly approved in 2022 by all the World Health Organization (WHO) Member States (WHO Intersectoral Global Action Plan for Epilepsy and Other Neurological Disorders [IGAP]) [6]. It is in the context of a well-known lack of health professionals, of health structures, of the existing underfunding and the current momentum for increased attention to neurological disorders that there is a high need for a sharp research agenda for neurological and brain research. There are increasing efforts by many recognized institutions to set up research agendas, and this reflects their multifaceted importance. The aim of a research agenda is to identify research priorities to catalyse funds to support scientific efforts to eventually improve diagnosis and treatment for people with neurological disorders, improve their quality of life, and consequently reduce the burden of neurological disorders. Creating a research agenda also allows us to reflect on the past research, to detect the current gaps, and to define the most highly prioritized future research goals. It is known that research agendas can sometimes be biased by researcher or commercial interests, leading to a mismatch between the priorities of donors, of researchers, and of people with neurological disorders and their caregivers [7, 8]. As such, there is a growing acknowledgment of the need to engage patients with neurological disorders as partners in research and to direct funding of those areas deemed most essential by end users. By asking not only experts such as neurologists and basic/translational/clinical neuroscientists, but also people affected by neurological disorders and their family and caregivers about the most urgent research needs, patient involvement can be acquired, resulting in a truly patient-centred vision on research priorities [9].

Research agendas often highlight the need for interdisciplinary research, broadening research possibilities. In addition, these agendas provide evidence for the necessity of increased funding and investments to maximize neuroscientific research and of developing new technologies for the realization of brain and neurological research in the context of identified priorities and epidemiological needs. Hence, in addition to providing research priorities, research agendas also serve as a framework to guide research funding agencies and sponsors in developing funding programmes [8].

In October 2022, the Shared Brain Research Agenda (SEBRA) was launched by the European Brain Council (EBC) and made available to researchers and policymakers [9]. It is an overarching roadmap developed by the members of EBC that includes preclinical to

basic and translational neuroscience as well as psychiatry, child neurology, and pharmacology and that serves as a good starting point to establish a general brain research agenda. The document provides a detailed description of preclinical research needs to better understand how the healthy and pathological brain functions, but it is less detailed on means to fight the burden and improve the diagnosis and treatment of neurological disorders. It therefore does not focus enough on prioritization of vitally important and necessary translational neurological advances.

To expand the focus of SEBRA, to tailor to the wide societal needs and to better serve the needs of neurological patients and their families, a European Academy of Neurology (EAN) working group conducted a scoping literature review to identify any existing research agendas applicable to neurology to highlight the current unaddressed research questions worldwide. EAN is active in research at different levels, with a recent emphasis on supporting education, international research collaborations, and implementing in its national Neurological Societies, the WHO IGAP and its own detailed Brain Health Strategy [10]. Following the review, a dedicated survey among the members of all EAN scientific panels (SPs), including residents, early career neurologists, and patient representatives, was performed, asking neurologists and patients about their views and perspectives on the current research priorities in terms of neurological diseases and related research gaps. An additional review by all EAN board members yielded additional input for the EAN SP survey. The literature review, in combination with the survey, forms the fundament for setting up a first comprehensive and specific neurological research agenda in Europe. It is intended as a priority-setting exercise and provides an opportunity for researchers, funding agencies, and sponsors to align their research goals in neurology with the values and needs of the patient community. However, it should be noted that this study focuses specifically on gaps within neurological care and on the impact of neurological disorders at the level of public health determined mainly by clinicians and scientists as well as patient organizations and their representatives. This study does not aim to determine the epidemiological scale of the burden and economic costs of neurological diseases, as these are the topic of other scientific studies supported by EAN [11].

METHODS

Scoping review

To gain insight into the current neurological research agendas, we searched for existing literature via the PubMed, James Lind Alliance, and Embase databases, covering the years 2018 to the date of search (1 January 2023). The following search terms were used: "neurology" and "research" and "agenda" or "research agenda", using the MeSH (Medical Subject Headings) terms and corresponding options in all databases. Articles that were included had to at least report on research agendas developed by a predefined expert panel and on methodology, covering any specific or general neurology topic. Papers from both international and national organizations, worldwide, were considered eligible. Only papers published in the English language were considered. Opinion papers, conference abstracts, papers without clear methodology and without predefined expert panels, and research agendas covering topics other than neurology (e.g., neuroscience) were excluded.

The initial screening of publications was done by the two first authors (P.B. and E.L.) independently; in the case of inconsistency, the final decision of inclusion of a paper was done following a discussion with a third author (K.A.). The following data were extracted from the eligible studies: title, reference number (PMID or other), subspecialty, database in which it was identified, authors, year of publication, country (if national) or the name of organization, and the main priorities identified.

Survey of the SPs

Following the scoping review, a qualitative approach was adopted, and a survey questionnaire was developed and discussed among the EAN board members before submission to the EAN SP members (Table 1). To collect the opinions of as many leading neurologists in Europe as possible, all members of the EAN SPs were invited to participate in the survey. They were asked to list the first three research priorities for the common and rare neurological diseases within and outside their subspecialty areas, and the main research gaps.

Follow-up survey

Based on the results of the first survey, a follow-up survey was set up with the purpose of obtaining more details on the subtypes of the seven most highly prioritized common and rare neurological

TABLE 1 List of EAN scientific panels.

1. Epilepsy
2. Movement disorders
3. Headache
4. Multiple sclerosis
5. Dementia and cognitive disorders
6. Neuroimmunology
7. Autonomic nervous system disorders
8. Neurogenetics
9. Neuroscience/translational neurology
10. ALS and frontotemporal dementia
11. Neuroepidemiology
12. Stroke
13. Muscle and NMJ disorders
14. Neuro-oncology
15. Sleep–wake disorders
16. Coma and chronic disorders of consciousness
17. Neuroimaging
18. Neurocritical care
19. Neurorehabilitation
20. Child neurology
21. Neuro-ophthalmology and -otology
22. Palliative care
23. Infectious diseases
24. Neurosonology
25. Pain
26. Clinical neurophysiology
27. Neurotraumatology
28. Higher cortical functions
29. Neuropathies

Abbreviations: ALS, amyotrophic lateral sclerosis; NMJ, neuromuscular junction.

diseases. More detailed questions were asked regarding the current research gaps specifically related to these diseases. The follow-up survey was completed by the co-chairs of the relevant SPs representing all panel members. An additional meeting was set up including all EAN board members to review the gathered data and adding relevant input regarding disease prioritization and identification of gaps. The follow-up survey was also sent to all patient representatives in the different SPs of EAN.

Organization of data and data cleaning

For the first survey, blank responses were deleted, diseases were checked for their correspondence to common or rare categories (using the orpha.net classification of rare diseases), and responses were reclassified between the gap section and disease categories as appropriate.

Given that the participants were asked to concentrate on diseases specific to the SP to which they belong, and taking in consideration the practical research applications of the survey results, the answers that were too broad to provide specific insight were deleted, which included the following answers: "neurodegenerative diseases", "stroke" (if reported by a member of the stroke SP), "epilepsy" (if reported by a member of the epilepsy SP), "diseases of cognitive disability", "dementia" (if reported by a member of the dementia SP), and "multiple sclerosis" or "multiple sclerosis therapy" (if reported by a member of the multiple sclerosis [MS] SP). In addition, the diagnostic procedures were deleted from disease categories.

Analysis of data

Descriptive statistics were used to analyse the responses of the participants in the first survey. The three main categorical variables (common neurological diseases, rare neurological diseases, research gaps) were categorized and, based on the frequency for each of the three priorities, the weighted mean value was calculated. Subsequently, the disease categories were ranked according to the frequency they were voted for. A similar approach was used to rank the gap categories. To examine whether the number of experts who voted from the corresponding disease panels influenced the final disease ranking (response bias), the responses of those panels were summed and the number was ranked from the highest to the lowest number of members who responded. We compared this ranking with the ranking of the diseases, using the Kendall coefficient of concordance [12].

RESULTS

Scoping review

The flowchart of the literature search is shown in Figure 1. Using the search strategy described previously, we identified 275 published papers in total. After removal of duplicates, 207 articles were screened by title and abstract, and 29 full-text articles were assessed for eligibility. From those, we identified a total of 21 eligible publications that could be considered research agendas related to

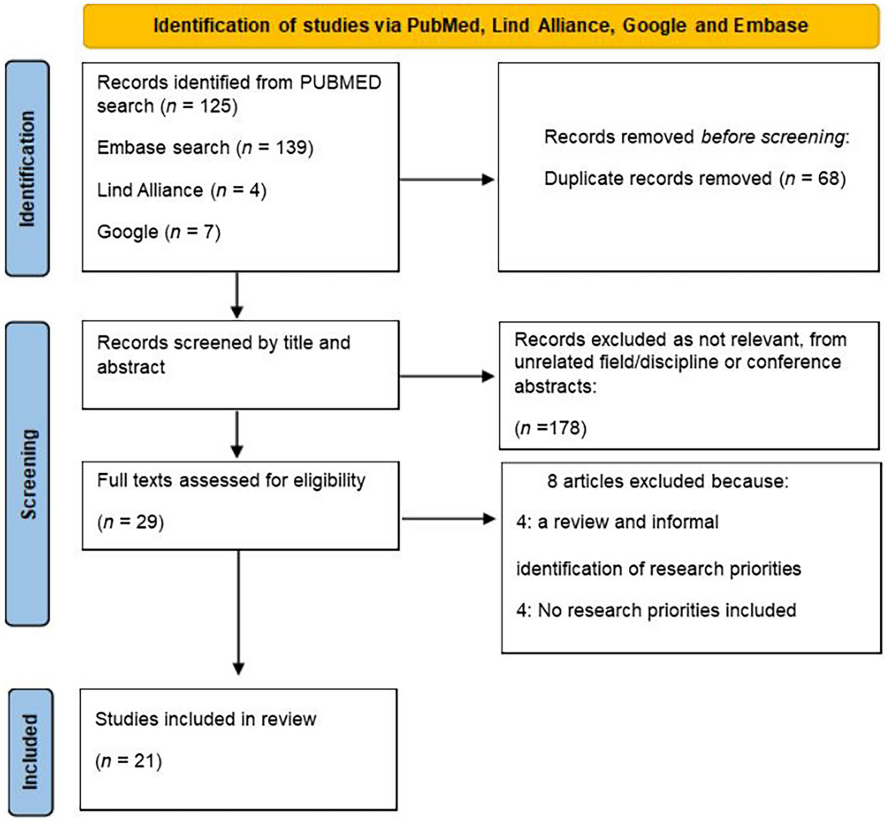

FIGURE 1 Prisma flowchart of the literature search results. PubMed example of the Medical Subject Headings (MeSH) terms used: ("neurology"[MeSH Terms] OR "neurology"[All Fields]) AND ((("research"[MeSH Terms] OR "research"[All Fields]) AND "agenda"[All Fields]) OR "research agenda"[All Fields]).

TABLE 2 Currently available research agendas.

Subspecialty	Publication	Country or (international) organization	Methods	Main findings
Stroke	Turner et al. [14]	United Kingdom	One-day meeting with 11 stakeholders to gather and prioritize research gaps	Top 3 (out of 11) research priorities: (i) Effective follow-up pathway for TIA/minor stroke patients (ii) Best way to identify which TIA/minor stroke patients will experience ongoing impairments (iii) Training/education of health care professionals to recognize post-TIA/minor stroke impairments
	Norrving et al. [15]	Europe ESO in cooperation with the Stroke Alliance for Europe	A steering committee guided 7 working groups (1 per domain). Per domain, 2 persons identified the research priorities.	Top 3 (out of 4) research goals: (i) Reduce the absolute number of strokes in Europe by 10% (ii) Treat 90% or more of all patients with stroke in Europe in a dedicated stroke unit as the first level of care (iii) Have national plans for stroke encompassing the entire chain of care
	Stinear et al. [16]	Not specified	Literature review	Top 3 suggestions for stroke-related clinical trial optimization: (i) Widening inclusion criteria to improve both the recruitment rate and the generalizability of results (ii) Narrowing inclusion criteria to reduce intersubject variability and enrich the sample (iii) Improving treatment fidelity and concealment, the use of domain-specific primary endpoint measures that are carefully aligned with the intervention's mechanisms of action, reducing barriers to research participation
	Hill et al. [17]	United Kingdom Stroke Priority Setting Partnership Steering Group	Two online surveys: 1 to identify research uncertainties, 1 to prioritize research uncertainties Online workshop	Top 3 (out of 10) priorities related to prevention, diagnosis, and treatment: (i) Best interventions for primary stroke prevention (ii) Recognition and early diagnosis of stroke and TIA (iii) Evaluation of risks and benefits of intracerebral hemorrhage treatments Top 3 (out of 10) priorities related to rehabilitation and long-term care: (i) Assessment of the impact of psychological effects and interventions to reduce them (ii) Assessment of communication problems and interventions to reduce them (iii) Evaluation of cognitive disfunction and interventions to reduce it
MS	Motl et al. [18]	USA National Multiple Sclerosis Society	Two 2-day meetings on wellness in MS A focal literature review A wellness research group to set priorities	Top 3 research questions related to: *Emotional wellness* (i) To what extent does resilience affect emotional health and/or the course of the disease? (ii) To what extent does positive psychology affect emotional health and/or the course of the disease? (iii) To what extent does stress management affect emotional health and/or the course of the disease? *Diet and nutrition* (i) To what extent do specific comprehensive diets, balanced diets, good nutrition, and/or specific nutrients affect physical health and/or the course of the disease? (ii) What are the most valid and reliable nutrient biomarkers to utilize in studies of diet? (iii) What role does the microbiota play in physical health generally and in the course of the disease specifically? *Exercise and physical activity* (i) To what extent does exercise/physical activity affect emotional health, physical health (comorbidities and secondary conditions), quality of life, and/or the course of the disease? (ii) What are the best approaches to exercise and physical activity for people with MS? (iii) What are the best methods for achieving successful "bench to bedside" translation of findings from exercise and physical activity research?

(Continues)

TABLE 2 (Continued)

Subspecialty	Publication	Country or (international) organization	Methods	Main findings
	Sumowski et al. [19]	US and European MS experts@	Evaluation of the current state of the field by MS researchers and clinicians and identification of important practical and theoretical challenges	Top 3 research priorities: *In understanding and measuring cognitive deficits* (i) Examine prevalence and expression of patient-level variability in cognitive profiles (ii) Research on cognitive–motor and cognitive–cognitive multitasking is needed to investigate real-world dual-tasking deficits (iii) Caution against presuming causal links among correlated functions extends to treatment expectation *For neuroimaging investigations of cognitive deficits* (i) Make a distinction between (a) neuroimaging correlates and (b) neural bases of cognitive deficits (ii) Investigation of isolated cognitive constructs (e.g., memory) rather than heterogeneous composites of multiple cognitive domains (iii) Development of multivariate models to better predict decline in separate cognitive domains is needed to develop clinically useful risk algorithms *For treatment and prevention of cognitive deficits* (i) Rigorous research designs to produce higher levels of evidence for including multicentre double-blind randomized controlled trials, with clear and specific a priori outcomes (ii) Essential guidelines for the conduct of high-quality cognitive intervention trials and adherence to these recommendations by investigators, post hoc reviewers, and journal editors (iii) Theoretical frameworks to build a science of cognitive rehabilitation in MS
	Bebo et al. [20]	US National Multiple Sclerosis Society in collaboration with international MS organizations and committees	Designing a roadmap together with the National Multiple Sclerosis Society's Scientific Advisory Committee, National Board of Directors, and the Pathways to Cures Task Force, composed of scientific thought leaders and people affected by MS A survey conducted in collaboration with the Accelerated Cure Project for Multiple Sclerosis	Pathways to Cures Research Roadmap: *Stopping the MS disease process* (i) An understanding of mechanisms driving the MS prodrome (ii) Longitudinal biomarker studies (iii) Research-based framework to select the best therapy for individual patients (e.g., precision medicine) *Restoring lost function by reversing damage and symptoms* (i) Physiologic mechanisms involved in regeneration and repair (ii) MS-specific outcome measures (biologic, imaging, and clinical) that are sensitive to regeneration and/or functional recovery (iii) Trial design that fosters the development of rehabilitation and wellness interventions *Ending MS through prevention* (i) Full knowledge of MS risk factors that are necessary and sufficient to cause MS and the time frame for exposure (ii) Availability of public health interventions that reduce or eliminate exposure to MS risk factors (iii) A complete understanding of the genetic and epigenetic contributions to MS risk and etiology
Movement disorders	MacDuffie et al. [21]	USA	Online surveys	Top 3 research questions regarding stigma in FND: (i) What is the prevalence of stigma in FND, and in which contexts does it occur? (ii) What is the clinical impact of stigma in FND? (iii) What are the best ways of reducing stigma in FND?
	Gilbert et al. [22]	USA Cerebral Palsy Research Network	Development of a community-drive research agenda together with clinicians, researchers, and the community	Top 3 (out of 10) priorities regarding dystonia in cerebral palsy: (i) Develop new treatments (ii) Assess rehabilitation, psychological, and environmental management approaches (iii) Compare effectiveness of current treatments

TABLE 2 (Continued)

Subspecialty	Publication	Country or (international) organization	Methods	Main findings
Neurodegenerative disorders	Schiess et al. [23]	Brain Health Unit at the World Health Organization	A multidisciplinary, sex-balanced, international consultation workshop	Top 3 (out of 6) goals to address global disparities: (i) Disease burden (ii) Advocacy and awareness (iii) Prevention and risk reduction
	De Miranda et al. [24]	USA National Institute of Neurological Disorders and Stroke National Institute of Environmental Health Sciences	Literature review	Top 3 (out of 5) priorities related to PD prevention *Preclinical/basic* (i) Examine environmentally relevant concentrations and routes of exposure (ii) Model combined environmental exposures (iii) Consider sex as a biological variable in toxicant exposure *Clinical/translational* (i) Measure PD incidence and its change globally (ii) Develop biological markers of exposure and identify during prodromal phase (iii) Perform whole-body autopsies to assess PD as a systematic disease
	Dams-O'Connor et al. [25]	USA National Institutes of Health	An AD-related dementias summit and follow-up meetings	Top 3 (out of 4) research gaps related to TBI related to dementia: (i) Encourage communication and interdisciplinary collaboration between TBI and dementia researchers (ii) Establish infrastructure to study TBI as a risk factor for AD/ADRD (iii) Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and associated clinical symptoms
	Martin et al. [26]	Europe	Literature review	Top 3 (out of 5) research gaps related to dementia: (i) Fragmented non-person-centred care pathways (ii) The culture of dementia care (iii) Limited knowledge and skill in dementia care
Epilepsy	Singh et al. [27]	Canada	Online surveys from stakeholders across Canada	Top 3 research priorities: (i) Genetic markers for diagnosis and treatment (ii) Concerns about living with the long-term effects of epilepsy (iii) Addressing knowledge gaps in etiology and treatment approaches
Disorders of consciousness	Hocker et al. [28]	Neurocritical Care Research Network	In-person meeting at the Fifth Neurocritical Care Research Network Conference	Top 3 research priorities regarding neurocritical care: (i) Continuous measurement of cerebral autoregulation (ii) Optimal dosing for central nervous system acting medications (iii) Valid cerebral blood flow measurement at the bedside
Pain	Gatchel et al. [29]	USA IPRCC and Office of Pain Policy at the National Institutes of Health	Priority setting via interdisciplinary work groups	Top 3 research priorities: (i) Develop safer opioids, new, nonopioid analgesics, and the first generation of disease-modifying agents (ii) Develop a research network (iii) Develop, evaluate, and improve models of pain care
Child neurology	British Paediatric Neurology Association [30]	United Kingdom British Paediatric Neurology Association	Stakeholder questionnaire Information evaluation Second survey to rank priorities Stakeholder workshop to identify top 10 priorities	Top 3 (out of 10) research priorities in child neurology: (i) Can early therapy interventions improve functional and developmental outcomes in babies experiencing brain injury during pregnancy or infancy? (ii) What are the most effective interventions to support sleep in children and young people with neurological conditions? (iii) How should we best manage emotional well-being in children and young people with neurological conditions?
TBI	Hutchison et al. [31]	Canada CTRC	Development of a collaborative research group that integrated a multidisciplinary network of TBI researchers	Top 3 priorities: (i) Create a collaborative Canadian research network (ii) Improve patient survival, functional outcome, and health through sustainable and scalable evidence-based practice implementation (iii) Strengthen the health care system for patients with TBI

(Continues)

TABLE 2 (Continued)

Subspecialty	Publication	Country or (international) organization	Methods	Main findings
Neuroimaging in FND	Perez et al. [32]	Worldwide International FND Neuroimaging Workgroup	Literature review International FND Neuroimaging Workgroup meeting	Top 3 (out of 10) research priorities: (i) More detailed categorical and dimensional characterization across neurological, medical, and psychiatric/psychological domains (ii) Patient controls across neurological, psychiatric, and medical diagnoses are needed to help delineate the specificity of observed FND findings (iii) Study designs should complement between-group approaches with relevant stratified between-group and within-group analyses
Aphasia	Ali et al. [33]	Worldwide Collaboration of Aphasia Trialists	Literature research Two-day research agenda-setting meeting	Top 3 (out of 5) highly prioritized research themes in aphasia (i) Evidence-based interventions for people with aphasia (ii) Effective interventions to support those communicating with people with aphasia (iii) Cross-linguistic assessment and core outcomes for aphasia research
Myalgic encephalomyelitis/ chronic fatigue syndrome	Tyson et al. [34]	United Kingdom	Online surveys and workshops	Top 3 (out of 10) research priorities: (i) Postexertional malaise (ii) Use of existing drugs for other conditions (iii) Diagnosis

Abbreviations: AD, Alzheimer disease; ADRD, AD and related dementias; CTRC, Canadian TBI Research Consortium; ESO, European Stroke Organization; FND, functional neurological disorder; IPRCC, Interagency Pain Research Coordinating Committee; MS, multiple sclerosis; PD, Parkinson disease; TBI, traumatic brain injury; TIA, transient ischaemic attack.

a range of neurological items and subspecialties [12–33]. The main reasons for exclusion in the title and abstract stage were the following: nonneurological topics, conference abstracts, informal or nonsystematic reviews, and opinion papers. In the full-text stage, papers were excluded because no research priorities were included, the paper was a review, or the paper lacked proper identification of research priorities.

Not a single general, overarching research agenda covering different neurological diseases in different neurological subspecialties could be found in the literature search. In addition, the number of published agendas per subspecialty was highly variable. Stroke, MS, and neurodegenerative disorders are the subspecialties in which the highest number of articles outlining research agendas have been published. For other subspecialties such as headache, rare neurological disorders, and sleep disorders, no recent research agendas were found. Although there was a comprehensive sleep–wake disorder research agenda published in 2015 [13], this could not be included in the literature review, as it does not fulfil the inclusion criteria (years covered: 2018–2023), showing the importance of regularly updating research agendas. The currently available research agendas with their top three reported research priorities are summarized in Table 2. A more extensive version of this table can be found in the Supplementary Materials.

Survey of the SPs

The survey was completed by members of the EAN SPs, all including representatives of patient organizations. Responses were obtained from all SPs with at least two and up to 12 responses from each SP. In total, 221 of 1969 SP members completed the survey (182 individual SP members, 21 members of the management groups, and 18 SP co-chairs), after a reminder was sent. Responses were classified according to 19 common and 15 rare neurological disease categories, and according to 12 research gap categories (Table 3). Responses that could not be assigned to one of the categories were added to the "unclassified" category.

Figure 2 shows the distribution of categorized common neurological disorders indicated by the EAN SP members with corresponding weighted percentages. The chart shows a top seven (weighted percentage ≥ 5%) highly prioritized common neurological disorder categories, with neuroinflammatory and neuroimmunology disorders being the first (16%), followed by headache and pain (13%), Alzheimer disease (12%), stroke (12%), movement disorders (10%), epilepsy (7%), and sleep/wake disorders (5%). The response bias analysis showed no correlation between the number of SP members who voted from the respective SP and the order of the top seven priorities (Kendall tau = 0.52, $z = 0.13$), indicating that there was no preference of the panels with the highest number of voters. Other common neurological disorders, amongst others neuro-oncological disorders, coma and disorders of consciousness, autonomic disease, neuropathies, and traumatic brain diseases, had a weighted percentage of <5%. An overview showing a more detailed priority setting of all common neurological disease groups can be found in Table S1.

Figure 3 shows the distribution of rare neurological disorder categories indicated by the EAN SP members with corresponding weighted percentages. The chart shows a top nine (weighted

TABLE 3 Overview of (common/rare) neurological disease and gap categories.

Common neurological disease categories	Rare neurological disease categories	Research gap categories
1. Headache and Pain 2. Alzheimer Disease 3. Stroke 4. Movement Disorders 5. Epilepsy 6. Unclassified 7. Sleep Disorders 8. Neuro-oncology 9. Coma and Disorders of Consciousness 10. Autonomic Neurosystem Disorders 11. Neuropathies 12. Traumatic Diseases 13. Neurodevelopmental Disorders 14. Intracranial Hypo-/Hypertension 15. Vestibular Diseases 16. Impact of Cancer Treatment 17. Disorders of the Muscle and Neuromuscular Joint Disorders 18. Spinal Cord Disorders 19. Neuroinflammatory/Neuroimmunological Disorders	1. Rare Neuroinflammatory/Neuro-immunological Disorders 2. Rare Movement Disorders 3. Motor Neuron Disease 4. Rare Forms of Dementias 5. Rare Primary and Secondary Headaches 6. Rare Vascular Disorders 7. Developmental Disorders With Epilepsy as a Major Sign 8. Disorders of Muscle 9. Rare Neuropathies 10. Rare Sleep Disorders 11. Rare Tumors 12. Unclassified 13. Rare Conditions of Coma and Disorders of Consciousness 14. Rare Intracranial Hypo-/Hypertension 15. Severe TBI	1. Treatment 2. Mechanism of Action 3. Diagnosis 4. Outcome and Prediction of Outcome 5. International Collaboration and Big Datasets 6. Prevention 7. Implementation and Availability of Advanced Scientific Techniques 8. Development of Guidelines and Implementation 9. Education and Training 10. Awareness 11. Epidemiology 12. Funding

Abbreviation: TBI, traumatic brain injury.

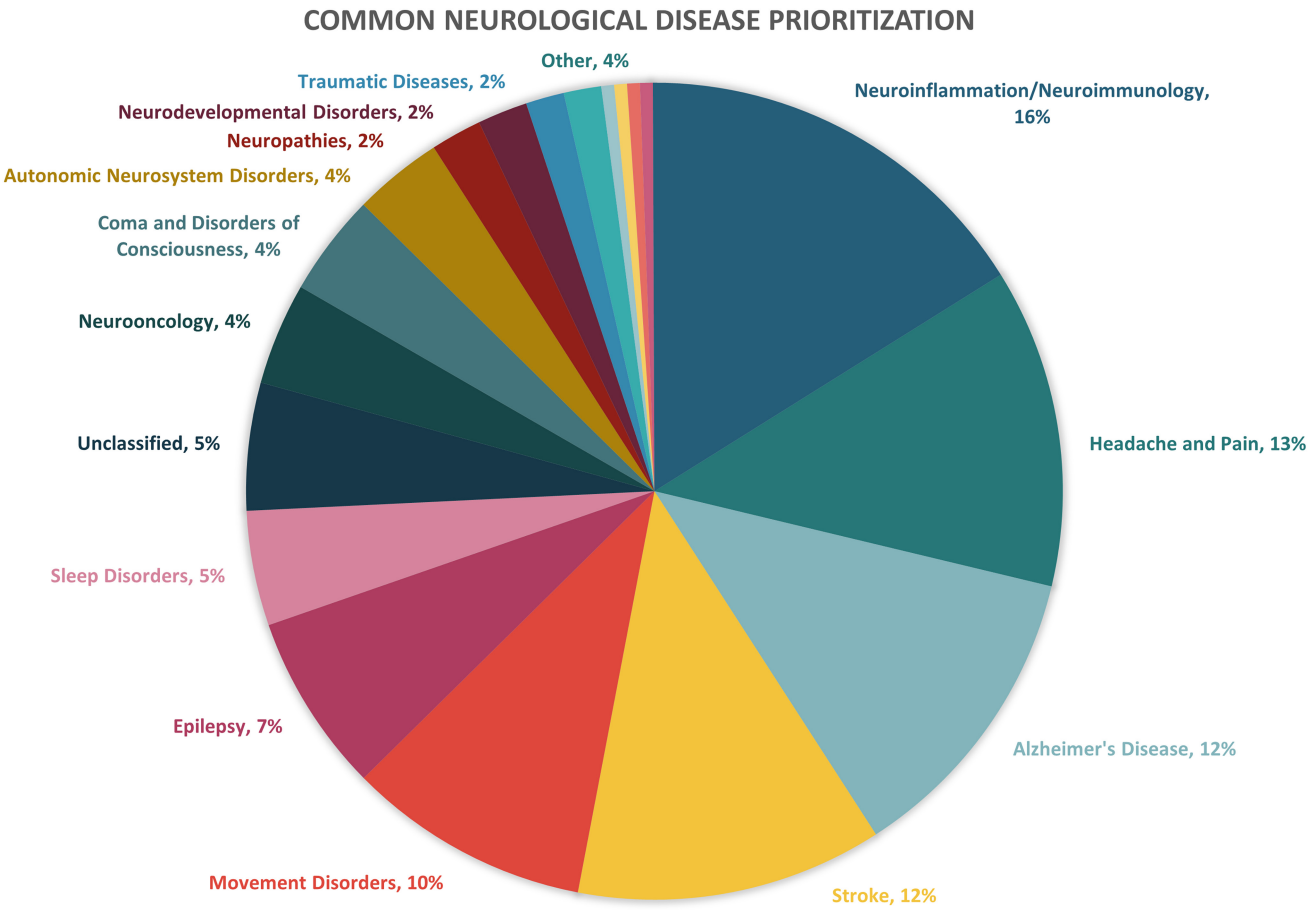

FIGURE 2 The distribution of categorized common neurological disorders.

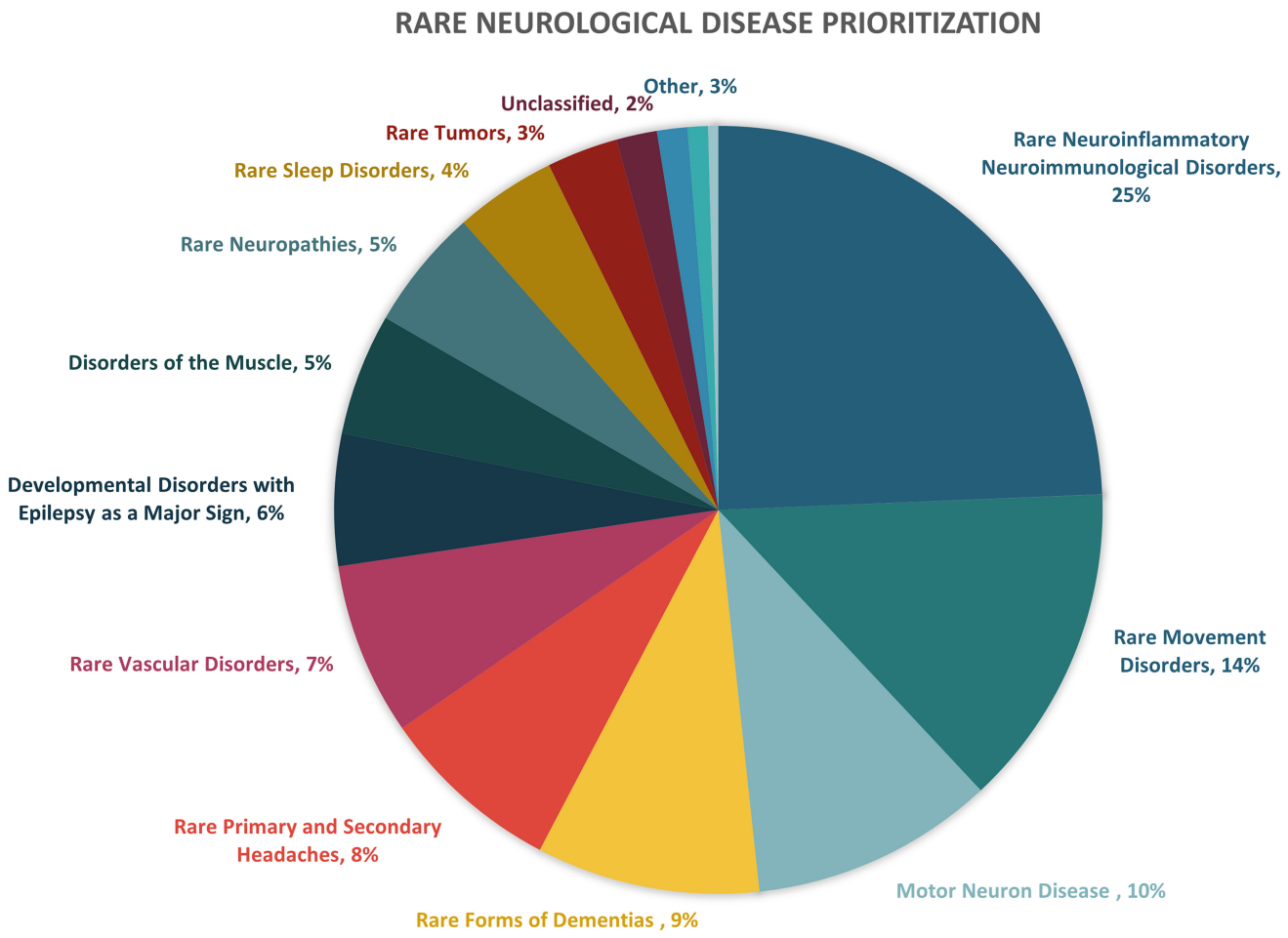

FIGURE 3 The distribution of rare neurological disorder categories.

percentage ≥ 5%) highly prioritized rare neurological disorders, with rare neuroinflammatory/neuroimmunology disorders (25%) being the first, followed by rare movement disorders (14%), motor neuron diseases (10%), rare forms of dementia (9%), rare primary and secondary headaches (8%), rare vascular disorders (7%), rare developmental disorders with epilepsy as a major sign (6%), rare muscle disorders (5%), and rare neuropathies (5%). An overview showing a more detailed priority setting of all rare neurological disease groups can be found in Table S2. Again, the response bias analysis showed no correlation between the number of SP members who voted from the respective SP and the order of the top nine priorities (Kendall tau = 0.29, $z = 0.45$), indicating that there was no preference of the panels with the highest number of voters.

Figure 4 shows the prioritization of current research gaps. The top six research gaps were the following: improving treatment (weighted mean = 31%), better understanding of underlying disease mechanisms (21%), improving diagnostic procedures (17%), improving outcome and prediction of outcome (8%), improving international collaboration and establishment of big datasets (6%), and prevention (5%). An overview showing a more detailed priority setting of all research gap categories can be found in Table S3.

Follow-up survey of the panel co-chairs, patient representatives, and board members

Based on the outcomes of the first survey, the following EAN SP chairs were asked to respond to the follow-up survey: movement disorders, infectious diseases, amyotrophic lateral sclerosis and frontotemporal dementia, neuroimmunology, stroke, epilepsy, dementia and cognitive disorders, headache, MS, and sleep/wake disorders. This selection of SPs was based on their affinity with the top seven common neurological disorders identified in the first survey. Rare neurological disorders were identified as a separate priority category. Additionally, all EAN board members provided comments and input on their priorities regarding the different neurological disease groups and overarching research priorities not specifically associated with one particular disease group. To maximally include the patient voice, the follow-up survey was also sent to all patient representatives in the EAN SPs.

Descriptive results of this follow-up survey with responses of the co-chairs are summarized in Table 4. Each panel indicated a top three prioritization of disease subtypes and research gaps related to the neurological disease relevant to their panel. A striking overlap

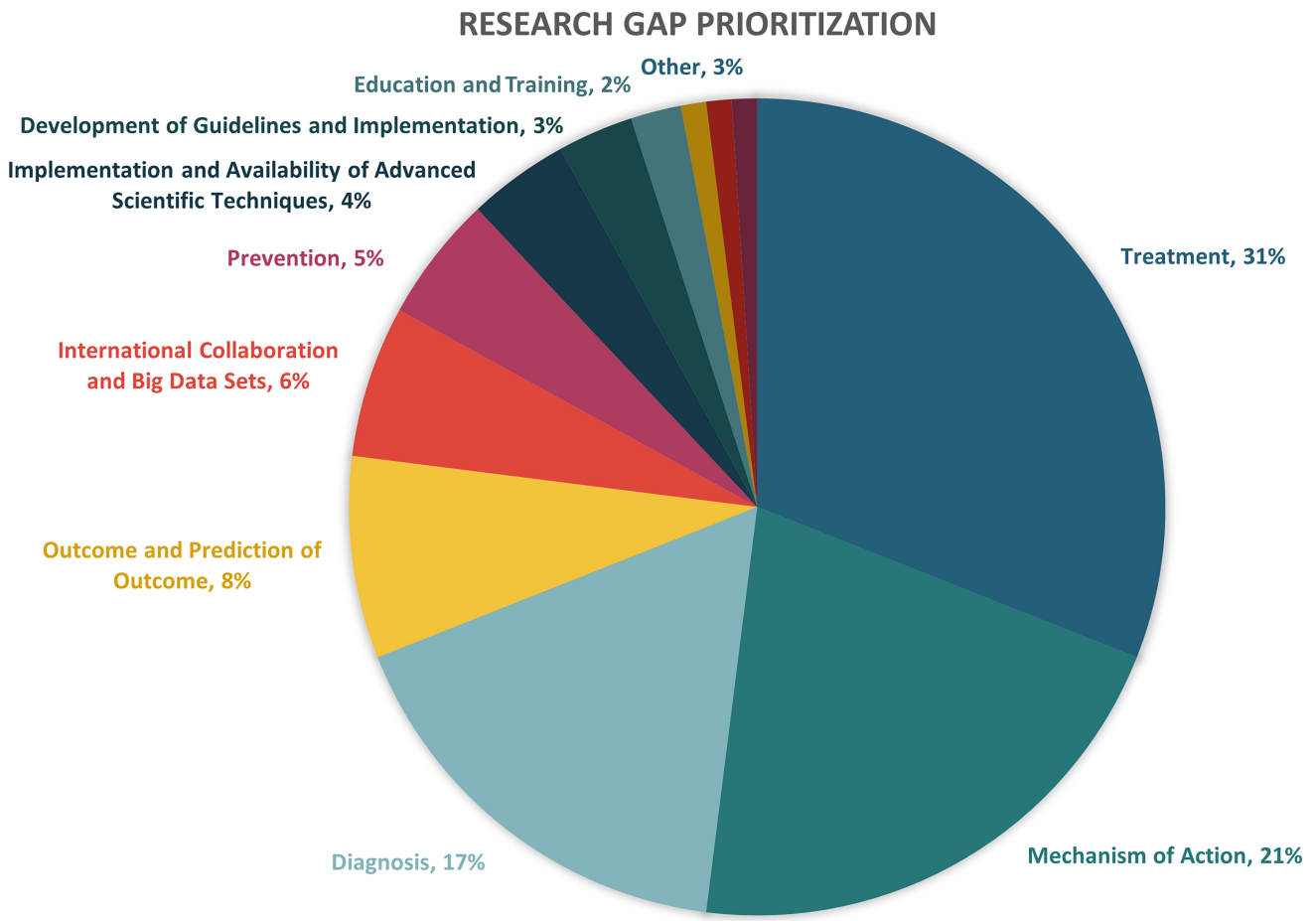

FIGURE 4 The prioritization of current research gaps.

between the indicated gap priorities of the first and second survey was found. In the second survey, nine of 24 (37.5%) gap priorities were related to investigating disease mechanisms, five of 24 (20.8%) to development of more targeted treatments, and four of 24 (16.7%) to improving diagnostic procedures. All three categories also belong to the top three identified gap priorities identified in the first survey (Figure 4), showing an alignment between the panel members and co-chairs of the SPs. Additional research gaps and further details on previously mentioned gaps were provided by board members (Table 4). In Table 5, the responses of the patient representatives, including members of the European Federation of Neurological Associations, are summarized.

DISCUSSION AND CONCLUSIONS

The main aim of this paper was to design a research agenda tailored to the needs of neurologists, neurological patients, and relevant stakeholders. The paper is composed of a quantitative (literature review) and a qualitative part (surveys) able to provide clear indications and targets.

The aim of the literature review was to screen the current research agendas in the field of neurology and to summarize the reported gaps per subspecialty. This review showed that the currently available agendas are mostly focused on one specific subspecialty, and that no general and comprehensive neurological research agenda, covering different neurological diseases in different subspecialties, exists to date. The lack of such a general neurological research agenda hampers gaining consensus on priority-setting across neurological disorders and related research gaps. Moreover, the absence of a generally shared and accepted neurological research agenda prevents providing effective guidance to research funding agencies, sponsors, and policymakers on how to better spend existing funding and possibly prioritize increased funding. Furthermore, a clear skewness in the number of published agendas across subspecialties has been detected. No agendas for rare neurological disorders were found. Even within the published agendas, there is a clear difference in number of agendas per subspecialty, with stroke and neurodegenerative disorders being the best covered subspecialties.

Subsequently, we endeavoured to set up a comprehensive neurological research agenda covering all subspecialties, adding a qualitative part to our research. To achieve this, a first survey was sent to all EAN SPs to identify the most highly prioritized neurological disorders and research gaps. Results showed that the top seven prioritized common neurological disorder categories are: neuroinflammatory/neuroimmunological disorders, headache and pain, Alzheimer disease, stroke,

TABLE 4 Top seven neurological disease groups, prioritization of subtypes of diseases, and research-identified common NDs, according to the panel cochairs and board members.

Disease group	Top 3 NDs	Top 3 research gaps	Detailed input given by the EAN board
Neuroinfections	(i) Severe CNS infections, pathogen-specific and adjunctive NICU therapies (ii) Emerging and imported CNS infections (iii) Fungal meningitis	(i) Understand role of virus in autoimmune pathophysiology (ii) Specific viral role in triggering autoimmunity (iii) Detection methodology of viruses	(i) Emerging neuroinfections (Zika, West Nile, COVID variants) (ii) Neurological complications of COVID-19, HIV/AIDS (iii) Lyme disease, tuberculosis, parasitoses
Neuroimmunological diseases	(i) Neurological complications of COVID-19 (ii) Long COVID-19 and neurological complications of COVID-19 vaccines (iii) Progressive neuroimmunology disorders	(i) Mechanisms of progressive neuroimmunology disorders (ii) Predictors of treatment response (iii) Interdisciplinary and translational research	
MS	(i) Highly active relapsing MS (ii) Disorders related to MS (iii) Radiologically isolated syndrome	(i) Mechanism of progressive MS (ii) Predictors of treatment outcome (iii) Interdisciplinary and translational research	(i) Genetic and environmental factors (ii) Early detection and predictive follow-up with biomarkers/imaging techniques (iii) Immunotherapies and cell therapies (iv) Quality-of-life and comorbidities (anxiety, depression, sleep disorders, etc.)
Headache/pain	(i) Mechanisms of cluster headache (ii) Mechanisms of tension type headache (iii) Mechanisms of migraine	(i) New treatment options for cluster headache (ii) Treatment for medically refractory cluster headache (iii) Predictors of treatment outcome	(i) Improved methods for measuring pain and assessing outcome (ii) Improved pharmacological and nonpharmacological treatments including novel drug targets, delivery methods, neuromodulation, and behavioural therapies
AD and dementias	(i) Prodromal phase of AD (ii) Mild cognitive impairment (iii) Mechanisms of AD	(i) Novel treatments for neurodegenerative diseases (ii) Biomarkers of neurodegeneration (iii) Novel treatment paradigms for AD	(i) Earlier detection and predictive follow-up measures (ii) Novel pharmacological and nonpharmacological treatments including new drug targets and neuromodulation (iii) Quality-of-life and comorbidities
Stroke	(i) Relationship of stroke and epilepsy (ii) Posterior circulation stroke (iii) Pathophysiological mechanisms of stroke	(i) Pathophysiological mechanism of stroke (ii) Cerebroprotection, recovery neuroplasticity after stroke (iii) Early prediction of individual functional outcome	(i) Improving stroke prevention (ii) Novel treatments and surgical interventions (iii) Improved rehabilitation and assistive techniques
Movement disorders	(i) Neuroprotection in neurodegenerative disease (ii) Prodromal Parkinson disease (iii) Dystonia	(i) Role of environmental factors (microbiome, toxic) in Parkinson disease (ii) Biomarkers for movement disorders (iii) Interdisciplinary and translational research	(i) Improved biochemical and imaging biomarkers (ii) Improved pharmacological therapies, surgical and gene therapies
Epilepsy	(i) Drug-resistant epilepsy (ii) Seizures/epilepsy in critical care (iii) Autoimmune epilepsies	(i) Predictors of treatment response (ii) Genetic epilepsies (iii) Novel treatment strategies for drug-resistant epilepsies	(i) Improved early seizure detection/prediction and wearables (ii) Improved drug targets, surgical techniques, and neuromodulation therapies

TABLE 4 (Continued)

Disease group	Top 3 NDs	Top 3 research gaps	Detailed input given by the EAN board
SWDs	(i) Neurobiology of SWDs in neurological patients (ii) Tele-sleep medicine (iii) Precision sleep medicine	(i) Health, costs, and psychosocial burden of SWDs in neurological patients (ii) SWDs as risk factors or first/main manifestation of NDs (iii) Sleep and SWDs as targets to modulate course/outcome of NDs (iv) Sleep and brain health	(i) Sleep disorders as risk factors and modulators of dementia/neurodegenerative disorders, stroke epilepsy, movement disorders, and other NDs (ii) Validation of new portable ambulator sleep–wake monitoring systems (iii) New biomarkers (and targeted treatment) of SWDs
Rare NDs	(i) Rare neuroinflammatory/neuroimmunology disorders (ii) Rare movement disorders (iii) Motor neuron diseases (iv) Rare forms of dementia (v) Rare primary and secondary headaches (vi) Rare vascular disorders (vii) Rare developmental disorders with epilepsy as a major sign (viii) Rare muscle disorders (ix) Rare neuropathies		
Overarching research priorities, not specifically associated with disease groups	(i) Systematic use of big datasets, pan-European collaboration for trials (ii) Exploring the potential of artificial intelligence (iii) Further development of telemedicine (iv) Establishing an updated role for general neurology ("comprehensive neurology") (v) Addressing diversity, equity, and inclusion issues as in relation to workforce and work environment of neurologists as well as treatment and diagnosis of NDs (vi) Exploring the influence of environmental and climate factors in patients and neurology practice (vii) Formalizing the role of the clinician scientist in neurology (viii) Researching preventive and other determinants of brain health		

Abbreviations: AD, Alzheimer disease; AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; EAN, European Academy of Neurology; HIV, human immunodeficiency virus; MS, multiple sclerosis; ND, neurological disorders; NICU, neonatal intensive care unit; SWD, sleep–wake disorder.

TABLE 5 Top three diseases and research gaps according to the patient representatives.

Panel	Society	Top 3 diseases	Top 3 gaps
Movement disorders	Dystonia Europe	(i) Restless legs (ii) Nonmotor symptoms (e.g., insomnia, depression) in movement disorders (iii) Joint collaborative research	(i) Awareness (ii) Training and education (iii) Multidisciplinary treatment
	Parkinson's Europe	(i) Parkinson disease (idiopathic and genetic) (ii) Parkinson disease (dementia) (iii) Dementia with Lewy bodies	(i) Prevention (ii) Training and education (iii) Funding
Headache	The migraine movement	(i) Migraine (ii) Cluster headache (iii) Tension type headache	(i) Education and training (ii) International big data on prevalence (iii) Implementation and availability of advanced scientific techniques
Pain	EFNA	(i) Stroke (ii) Alzheimer disease (iii) Parkinson disease	(i) Implementation and availability of advanced scientific techniques (ii) Timely and adequate treatment (iii) Timely and adequate diagnosis
Sleep–wake disorders	EFNA	(i) Restless legs syndrome (ii) General insomnia (iii) Daytime sleepiness	(i) Funding (ii) Education and training (iii) Awareness
Palliative care	EFNA	(i) Pain in neurological conditions (ii) Sleep disorders in neurological conditions (iii) Psychological and psychiatric problems in neurological conditions	(i) Fast access to diagnosis (ii) Development and implementation of guidelines (iii) Epidemiology

Abbreviation: EFNA, European Federation of Neurological Associations.

movement disorders, epilepsy, and sleep/wake disorders. According to all relevant stakeholders, ranging from experts in the field to patients, these neurological diseases are to be researched with the highest priority. According to the literature review, stroke, MS, and movement disorders have already received high levels of attention in the existing subspecialty literature. This suggests that headache and pain, Alzheimer disease, epilepsy, and sleep/wake disorders are neurological diseases that need to be researched with the highest priority. Equally important is to include rare neurological disorders in future research agendas and to identify prioritization among these disorders. This will increase the awareness of rare neurological diseases and the need to research underlying disease mechanisms to develop new treatments, as these diseases are often underrepresented in previous research agendas. A focus on investigating the nine main rare neurological disorders in this agenda is definitely an important first step, but the research focus should reach beyond these nine disorders.

Prioritizing research into specific neurological disorders, however, was not considered enough, as it is highly relevant to also identify the main research priorities beyond specific neurological diseases and to tackle existing research gaps. The survey revealed that the top six global research gap categories for neurology are, in ranking order: improving treatment options, improving the understanding of underlying disease mechanisms, improving diagnostic procedures, improving outcome and prediction of outcome, improving international collaboration and establishment of big datasets, and prevention. It is noteworthy that prevention is included in this list of top research priorities covering needs and gaps, as there is now rising interest in brain health and increased understanding of preventive measures for neurological disorders.

For the European neurological community, it seems clear that more research is needed to explore and develop new treatment options, especially for people suffering from the most highly prioritized diseases. Remarkably, investigating the underlying mechanism of neurological disorders was identified as the second most prioritized research need, showing that for neurologists, who mostly have a clinically oriented background and training, it is important to have a translational and multimodal approach to neurology. Our findings confirm that mechanistic and preclinical research is deemed relevant to understand the neurobiological and neurophysiological underpinnings of neurological disorders. The full understanding of these diseases from bench to bedside can lead to more precise and effective prevention, diagnosis, and treatment, in particular precision and personalized medicine.

To further examine the specific research questions related to the top seven common neurological disorders identified by this first survey, a follow-up survey was sent to the EAN SP co-chairs and patient representatives related to each category of this top seven. The results represent the most relevant subtypes of one of these top seven disorders and the corresponding gaps. Remarkably, there was a clear overlap between the top three gap categories identified by the first survey and the research gaps indicated by the SP co-chairs. The validity of the top seven list was again confirmed by the members of the EAN board, and some additional research gaps and more detailed research topics (both disease-specific and overarching) were listed, adding to a higher level of granularity of the present research agenda. Table 4 may serve as a formal shortlist of current clinically relevant research topics validated by a large number of representative clinicians,

patients, clinical researchers, and leaders in European neurology. Table 5 shows in more detail patients organizations' research priorities that have been considered and listed so as to empower global results of the EAN research agenda. Remarkably, (lack of) education and training are the most frequently reported gaps by patient representatives, which is quite different from the results on gap prioritization of the first survey (Figure 4). This shows the importance of sharing and discussing research goals between all relevant stakeholders as well as incorporating patients' opinions, as this leads to new important insights.

The relevance of the present EAN strategic research agenda compared to SEBRA is clear-cut. It truly is the first neurological research agenda to comprehensively cover all gaps and needs, to clearly suggest detailed research priorities, formulated and validated by a representative sample of the neurological community consisting of clinicians, clinical scientists, and patient representatives.

The present research agenda also has clear limitations. The methodology of administering surveys can only be expected to yield qualitative rather than quantitative outcomes. Although no response bias was detected and answers were obtained from all SPs, the surveys were only completed by part of all EAN SP members, which may limit the representativeness of our sample. Despite the inclusiveness of the panels in terms of age and gender and the representation of patients, we must be aware of bias that could be present due to the difference in response rate among different SPs. Societally relevant issues such as attention to sustainability and environmental factors relevant to neurological disorders were not specifically addressed in the present research agenda. It is noteworthy that non-disease-related gaps and needs have been considered but not listed by SP members, as questionnaires were mainly disease-oriented; however, SP chairs and EAN board members, in line with recent publications, white papers, and roadmaps relevant to these issues [35, 36], have clearly labelled diversity, equity, and inclusion as well as environmental and climate change-related research as high priorities.

It is also important to note that although patients are represented in most of the SPs, the majority of members of such panels and respondents to the survey were clinicians or clinician scientists. To counteract this and to maximally incorporate the patient voice in this agenda, the follow-up survey was sent directly to all patient representatives of the EAN SPs, and a patient and advocate for patient inclusion in research co-authored the manuscript. We truly believe that setting up a research agenda is an interactive process, in which this agenda can serve as a fundament. Additional steps will be needed to achieve an exclusively patient-centred agenda in the future.

To our knowledge, this work is the first European global neurological research agenda identifying research priorities across neurological subspecialties. In addition to existing partial research agendas, the present EAN neurological research agenda can serve as a clinically and societally relevant roadmap for donors, funding agencies, researchers, and clinicians in the field of neurology. It will also help clinicians to align their research goals with the values and needs of the patient community. Researchers, clinicians, policymakers, patients, and other interested stakeholders should consider implementing this agenda when interacting with agencies involved in supporting brain and neurological research as well as when dealing with efforts to reduce the burden of neurological disorders in Europe. It is our firm belief that implementing this research agenda should eventually lead to closing the funding gap for neurological research and thus contributing to reduce the global burden of neurological disorders. Research has no borders.

AUTHOR CONTRIBUTIONS

Paul Boon: Conceptualization; investigation; writing – original draft; writing – review and editing; project administration; supervision; data curation; validation; resources; methodology. **Emma Lescrauwaet:** Project administration; methodology; writing – original draft; writing – review and editing; investigation; validation; resources; data curation; visualization; conceptualization; formal analysis. **Katina Aleksovska:** Investigation; visualization; writing – original draft; writing – review and editing; formal analysis; data curation; methodology; conceptualization. **Maria Konti:** Writing – original draft; visualization; formal analysis; data curation; methodology; investigation; writing – review and editing; conceptualization. **Thomas Berger:** Writing – review and editing; conceptualization. **Matilde Leonardi:** Writing – review and editing; conceptualization. **Tony Marson:** Writing – review and editing; conceptualization. **Ulf Kallweit:** Conceptualization; writing – review and editing. **Elena Moro:** Writing – review and editing; conceptualization. **Antonio Toscano:** Writing – review and editing; conceptualization. **Irena Rektorova:** Writing – review and editing; conceptualization. **Michael Crean:** Writing – review and editing; supervision; project administration; methodology; conceptualization; investigation; writing – original draft; validation; resources. **Anja Sander:** Writing – review and editing; conceptualization. **Robert Joyce:** Writing – review and editing. **Claudio Bassetti:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors state explicitly that there is no conflict of interest to disclose in connection to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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