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Technology-Enabled Recreation and Leisure Programs and Activities for Older Adults With Cognitive Impairment: Rapid Scoping Review

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Abstract

Background: Recreational and leisure activities significantly contribute to the well-being of older adults, positively impacting physical, cognitive, and mental health. However, limited mobility and cognitive decline often impede access to these activities, particularly for individuals living with dementia. With the increasing availability of digital technologies, there is a rising interest in using technology to deliver recreation and leisure activities for cognitively impaired individuals, acknowledging its potential to provide diverse experiences. The COVID-19 pandemic further highlighted the need for virtual program delivery, especially for individuals in long-term care settings, leading to the development of tools like the Dementia Isolation Toolkit aimed at supporting compassionate isolation. To better support future implementations of the DIT, our rapid scoping review explores evidence-based, technology-enabled recreation programs for older adults with cognitive impairments, which promote well-being.

Objective: We conducted a rapid scoping review of published peer-reviewed literature to answer the following research question: What recreation and leisure programs or activities are being delivered using technology to adults living with dementia or another form of cognitive impairment?

Methods: In total, 6 databases were searched by an Information Specialist. Single reviewers performed title or abstract review, full-text screening, data extraction, and study characteristic summarization.

Results: A total of 92 documents representing 94 studies were identified. The review identified a variety of technology-enabled delivery methods, including robots, gaming consoles, tablets, televisions, and computers, used to engage participants in recreational and leisure activities. These technologies impacted mood, cognition, functional activity, and overall well-being among older adults with cognitive impairments. Activities for socializing were the most common, leveraging technologies such as social robots and virtual companions, while relaxation methods used virtual reality and digital reminiscence therapy. However, challenges included technological complexity and potential distress during reminiscing activities, prompting recommendations for diversified

research settings, and increased sample sizes to comprehensively understand technology's impact on leisure among this demographic.

Conclusions: The findings suggest that technology-enabled recreational activities, such as socializing, relaxation and self-awareness activities, music and dance, exergaming, and art, can positively impact the mood and overall well-being of older adults with cognitive impairment. Future research should embrace a more inclusive approach, integrating design, diverse settings, and a broader sample of older adults to develop technology-driven leisure activities tailored to their unique needs and promote their effective use.

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KEYWORDS

scoping review; review methods; review methodology; knowledge synthesis; synthesis; syntheses; scoping; rapid review; rapid reviews; gerontology; geriatric; geriatrics; older adult; older adults; elder; elderly; older person; older people; ageing; aging; gerontechnology; technology; recreation; recreational; leisure; hobby; hobbies; cognitive; MCI; Alzheimer; dementia; digital health

Introduction

Background

Participating in recreational and leisure activities is a significant contributor to the health and well-being of older adults [1,2]. Recreation and leisure activities include pursuits such as dancing, walking, singing, or playing a musical instrument, creative pastimes such as painting, pottery or woodworking, and a wide variety of sports and games. Recreation and leisure activities can be enjoyed alone or as part of a group and have been shown to positively benefit older adults' physical and cognitive function and mental health [3].

In later life, a range of factors can reduce opportunities and access to recreation and leisure pursuits including limited mobility [4] and cognitive loss [5]. People living with dementia, for example, face multiple barriers to continued participation in recreation and leisure activities [6-8] due to progressive cognitive decline. Consequently, limited access to recreation and leisure activities negatively impacts people living with dementia or other forms of cognitive impairment through lack of socialization and stimulation [9,10].

Technology-Enabled Delivery of Recreation and Leisure Activities

The use of technology to deliver recreation and leisure activities for people living with impaired cognition, is becoming more commonplace [11-15], with the recognition that technology can facilitate in-person leisure as well as new forms of uniquely digital experiences [16,17]. The rise in interest may reflect the increasing availability of digital technologies, from tablets to robots. Touchscreens, for instance, are particularly accessible for people living with dementia as they provide immediate feedback through touch [13]. As such, touchscreen tablets and larger devices have been successfully used to deliver a variety of recreation activities including games [13], reminiscing activities [18,19], and music [20]. Touchscreens have also been tested in the form of telepresence robots—simple, nonhumanoid frames with a touchscreen that can be controlled to move on flat surfaces [21]. Art is another popular target for technology for people living with dementia including virtual reality [22] and virtual reality tours of art galleries [23], making and viewing art together on tablets [24,25] and art therapy [11,26]. More energetic activities using motion-based game systems such as the Wii [27] and Xbox [28] have been shown to not only promote physical activity but also socialization and enjoyment [29].

COVID-19 Heightened the Need for Web-Based Program Delivery

The impact of a lack of recreation and leisure activities for people living with cognitive disabilities was underscored during the COVID-19 pandemic. Compromised cognitive functioning, language, insight, and judgment associated with dementia impact the ability of individuals to understand and appreciate the necessity of isolation and to voluntarily comply with isolation procedures [30]. The enforcement of isolation protocols to prevent the transmission of the virus during the pandemic drastically reduced recreation and leisure activities for people living with dementia [31]. Long-term care (LTC) home staff faced significant challenges in enforcing these protocols, leading to ethical dilemmas and moral distress as they navigated the balance between ensuring safety and promoting the well-being of residents [31-33]. At this stage of the pandemic, outbreaks of infectious diseases, including COVID-19, remain frequent events in LTC homes, and there is an ongoing need for the delivery of recreation opportunities for residents in isolation.

The Dementia Isolation Toolkit (DIT) was developed to support compassionate, safe, and effective isolation of people living with dementia in LTC settings and contains a series of tools designed to provide ethical, legal, and clinical guidance to support decision-making (34,35). It also includes methods and approaches, including those that are technology enabled, to support safe isolation for individuals living with cognitive impairment, ensuring their dignity and well-being. Given the wide variety of technologies and digital activities being developed and tested for older adults living with impaired cognition [12,15,36], we conducted a rapid scoping review to identify technology-enabled recreation and leisure programs or activities that are being delivered to older adults living with cognitive impairment. Our aim was to identify programs with supporting evidence of efficacy, which might complement the DIT and facilitate its adoption and use in LTC. While reviews exist focusing on technological interventions for individuals

living with dementia, they often focus on loneliness rather than other benefits of recreation [15].

Methods

Research Design

We conducted a rapid scoping review of published peer-reviewed literature. A rapid review was selected to allow us to generate timely results to inform the design of novel digital interventions to deliver recreation and leisure activities for people living with cognitive impairment [37]. However, we combined rapid review methodology with scoping review methodology to allow us to map the key issues or topics in a research area where the literature has not been reviewed comprehensively, and many different study designs may be applicable [38,39]. This review was conducted following Arksey and O'Malley's [40] scoping review methodology and was informed by the Cochrane guidance on rapid reviews [41]. The review is reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework [42] (see Multimedia Appendix 1).

Step 1: Identifying the Research Question

Based on the knowledge and experience of the multidisciplinary DIT team and familiarity with the literature on technology for recreation and leisure for persons living with dementia, we identified the following research question: What recreation and leisure programs or activities are being delivered using technology to adults living with dementia or another form of cognitive impairment?

Step 2: Identifying Relevant Studies

On January 20, 2021, the following health and technology databases were searched using a search strategy developed by the research team, which included an Information Specialist (JB):ACM Digital Library, CENTRAL (Ovid), CINAHL (EBSCO), Embase (Ovid), IEEE Explore, and MEDLINE (Ovid). No limitation was set on publication year. When possible, searches were limited to include only English-language publications and primary research articles.

The searches for CINAHL (EBSCO) and MEDLINE (Ovid) were then updated on April 11, 2024 (see Multimedia Appendix 2), using the same search strategy. The decision for selecting these 2 databases was done by analyzing included studies from the original search to determine from which databases the studies were retrieved. All the studies selected for inclusion were retrieved from these 2 databases, and thus, to expedite the process of the update, an informed decision was made to focus updates on these 2 databases.

In addition to comprehensive database searching, the reference lists of included studies were reviewed for relevant studies.

Stage 3: Study Selection

The study selection process consisted of 2 stages: first by screening titles and abstracts; and second, by full-text screening. To be eligible for inclusion at both stages, the article must have reported on primary research that included an evaluation of a technology and explored the experiences of older adults with cognitive impairment using the technology. The technology must have been used to deliver or enable recreation and leisure programs. Inclusion and exclusion criteria are presented in Table 1.

Inclusion criteria were refined iteratively throughout each stage of the screening process (title and abstract, full text), as recommended by Levac et al [43]. First, all team members screened the same subset of titles and abstracts to calibrate the inclusion criteria. Then, one team member screened approximately 25% of the titles and abstracts [41]. All team members screened another subset of titles and abstracts to further refine the inclusion criteria [41]. Finally, the remaining approximately 75% of the titles and abstracts were divided amongst 5 team members and individually screened.

All team members reviewed an initial subset of full texts to calibrate our inclusion criteria. Twenty percent of the remaining full-text articles were double reviewed, and discrepancies were resolved through discussion.

Table 1. Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Language of the studies	English	Languages other than English
Study design	• Empirical research articles (eg, qualitative, randomized controlled trials [RCTs], quasi-experimental designs, observational studies [eg, cohort studies, case-control studies), cross-sectional studies, longitudinal studies, pre-post studies, mixed methods studies)– reporting on an evaluation focused on older adults. • Must explore experiences of older adults.	• Nonempirical study designs, such as reviews. • Exclude conference abstracts. • The evaluation should not solely be on the technology or the caregivers.
Intervention	• Recreation and leisure (eg, arts-based interventions, music, dance, games, exergaming, recreational activities, recreation, leisure activities, creative, games, exergaming, cognitive stimulation therapy, socializing, and social interactions) "program" or "activity" for adults aged 18 years or older with cognitive impairment.	• The intervention should not focus on the assessment, monitoring or detection of cognitive impairment (if no game component or reference to experience).
Mode of delivery	• Delivered using technology (eg, app, device, platforms, robot). • Technology must have leisure component.	• Technology that is used to monitor or detect cognitive impairment.
Population	• Adults aged 50 years or older with cognitive impairment including (but not limited to) dementia, Wernicke encephalopathy, delirium, amnestic, Alzheimer disease, organic brain disease or syndrome, benign senescent forgetfulness, Binswanger, Korsakoff syndrome, stroke-related cognitive impairment, Wilhelmsen-Lynch disease, aphasia, Benson syndrome, Huntington's disease, mild cognitive impairment or disorder, Creutzfeldt Jacob disease, or Parkinson disease	• The populations cannot be at risk for cognitive impairment prevention (ie, older adults who are not currently cognitively impaired). • Internet gaming disorder and addiction or alcoholism-related disorders are excluded.

Stage 4: Charting the Data

Our data were charted and sorted according to areas of potential relevance to the research questions including (1) country in which the study was conducted; (2) study site; (3) type of activity; (4) sample size; (5) population age range; (6) sex, if available; (7) type of cognitive impairment; (8) research question or aims; (9) study methods; (10) description of technology; (11) outcomes or findings; and (12) feasibility, as described by study authors. Double data extraction was conducted on the final set of articles included in this review. Using Microsoft Excel, 2 research assistant team members charted the data. A third team member reviewed the charting and coded the data extraction into categories, where relevant.

We did not assess the quality of included studies, as quality assessments are neither required nor appropriate for scoping review methodology [39,43].

Stage 5: Summarizing and Reporting the Data

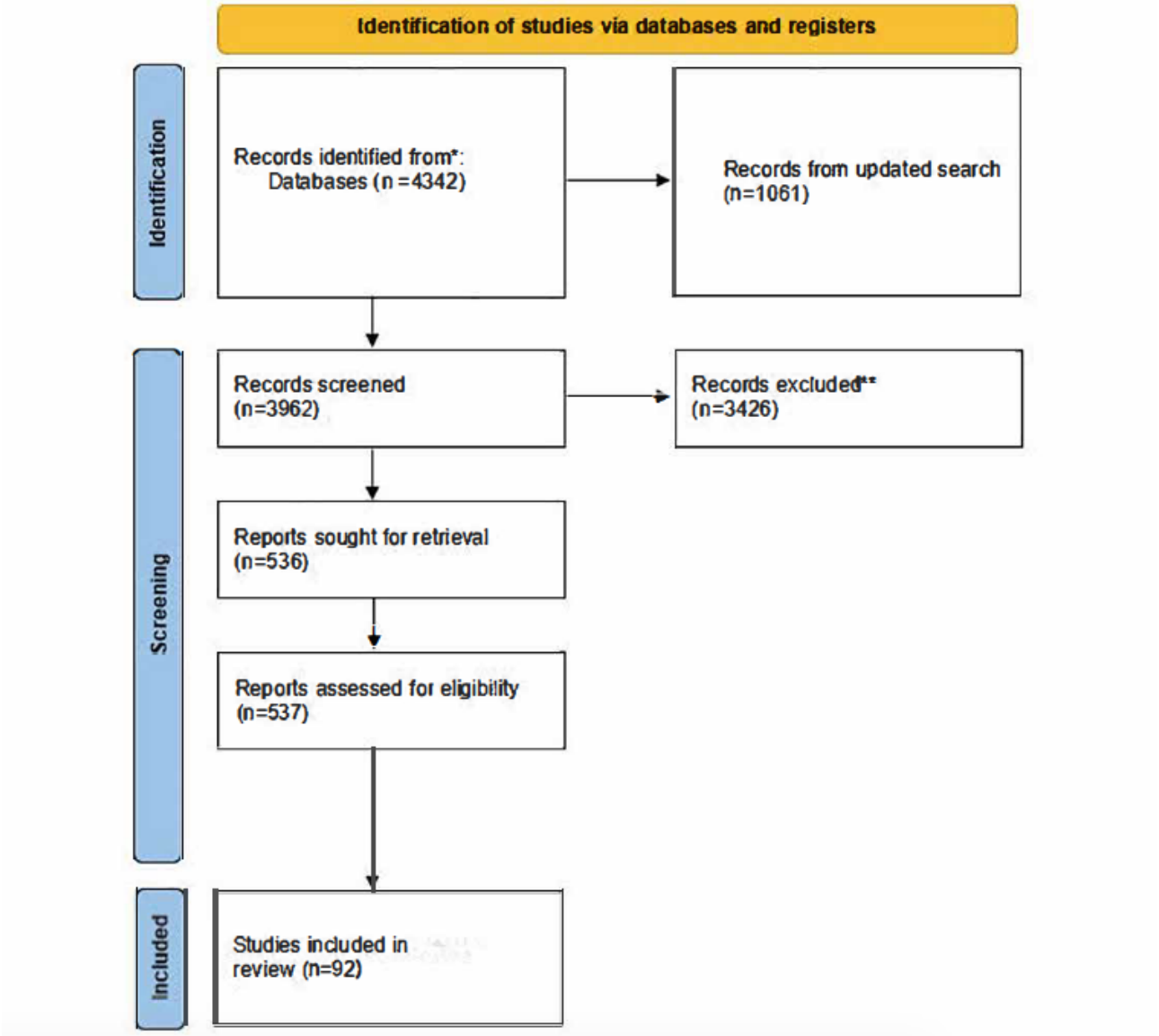
Data were organized numerically using descriptive statistics and summarized using a narrative descriptive synthesis by members of the research team that included gerontologists, nurses, psychologists, and health researchers who provided their perspectives on the findings [44]. The constructs considered for review included age, patient population, technology used, and outcomes.

Results

Overview

Our initial search yielded 4342 results, with a further 1061 results following a search update. Following deduplication, 3962 results were eligible for screening. The screening process resulted in a total of 92 documents, 61 from the original searches, and an additional 31 documents in the updated search. See Figure 1 for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [42].

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Publication dates ranged from 2000 to 2022, with most (57/92, 62%) published between 2016 and 2021, which confirmed an expected interest in the topic over time. Of these 92 documents, 1 paper [45] reported on 3 studies, resulting in a total of 88 studies for analysis. The studies were conducted in multiple countries; mostly in the United States, Canada, and the United Kingdom. Table S2 in Multimedia Appendix 3 outlines the key characteristics of the included studies.

From these studies, 46 employed mixed methods (46/94, 49%), 28 were qualitative (28/94, 30%) and 21 were quantitative (21/94, 22%). Among the qualitative studies, the most common methods for data collection were interviews (9/28, 32%) [45-53] and observational techniques (15/28, 54%) [28,45,47,48,51,54-63]. Among the quantitative studies, the most common methods of data collection consisted of experimental data collection (16/21, 76%) [64-79] and surveys or questionnaires (4/21, 19%) [74,80-82].

Participants Targeted

The sample sizes ranged from 1 [54,81,82] to 139 [84] participants. In total, this review contained 2332 participants. Ages ranged from 50 [85] to 104 [86] years. There were inconsistencies with reporting patient demographics with 11 studies (11/94, 12%) failing to report age range or mean [48,51,56,64,65,71,87-91]. Most studies indicated that they recruited both male and female participants (65/94, 69%). The primary clinical indicator for participants was dementia (unspecified) (60/94, 64%), followed by Alzheimer disease (9/94, 9.5%), and mild cognitive impairment (12/94, 13%). An additional 8 studies (10/94, 11%) reported a mixed form of dementia. Most participants were recruited from either residential care (eg, assisted living) facilities (40/94, 42.5%), day care (eg, senior) centers (19/94, 20%), home (13/94, 14%), hospital inpatients (4/94, 4%) or other health care settings (2/94, 2%), and hospice (1/94, 1%). Only a few studies (14/94, 15%) reported on the ethnicity of participants [24,52,54,57,63,69,83,86,92-97], with mostly White participants participating in all but 1 study [92]. Table S3 in Multimedia Appendix 4 outlines the key characteristics of participants.

Types of Leisure Activities

The types of technology-enabled recreational and leisure activities for older adults with cognitive impairment were categorized as follows: (1) socializing; (2) relaxation and self-awareness; (3) music and dance; (4) exergaming; (5) video or audio (nonmusic) entertainment; (6) playing games; and (7) art. Socializing (46/94, 49%) [48,50,53,58,63,65,66,70-72,76,80,82,84,86,91-94,96,98-114] was the most commonly used recreational and leisure activity; 20 (20/94, 21%) studies used a combination of activities. Examples of how socializing activities were fostered by technology included the use of social (companion [111]) robots (eg, PARO [82,86,102,106,109,110] and MARIO [99,103,113]), online pet companions [101], social recognition watch [93], and Skype on Wheels [87]. According to some articles, these technologies facilitated social engagement as they recognized the gestures, emotions, stimuli, and speech of older adults and engaged them in active conversation [66,98,104,108].

The prevalence of socialization activities was followed by relaxation and self-awareness activities (22/94, 22%) studies [50,52,63-65,68,75,76,81,88,92,94,98,100,102,111,115-121]. These activities were facilitated through various means including virtual reality [65,115,116], computer activities [94], digital life storybooks [121], digital reminiscence therapy [75,111]). Table S4 in Multimedia Appendix 5 outlines the category of activities used in each study.

Types of Technological Delivery

There was a wide range of technology-enabled delivery methods. Most technologies were commercially available. Table S5 in Multimedia Appendix 6 outlines the origin of technology used in each study indicating whether it was obtained commercially (57/94, 61%), developed in-house (17/94, 18%), or a combination of both (20/94, 23%). However, it is important to note that the studies included in the analysis did not provide sufficient information regarding the technological development process.

In addition to robots, as previously mentioned, some studies used game consoles, including those that accurately track the participants' arm, hand, and body movement as well as facial expressions [62,74,84,122,123]. Some interventions were rooted in artificial intelligence to address social and emotional needs by engaging with older adults with speech and touch [46,65,80,98,99,113,124]. Some interventions used tablets [24,49-51,58,60,75,83,85,100,101,105,114,116,119,124-128], televisions [47,49,62,64,68,73,88,120,121], or computers [61,87,90,92,94,95,98,115,116,129,130] to engage participants in auditory and visual activities by stimulating cognition such as through memory stimulation. Other studies used technologies that facilitate simulated and interactive experiences with near-eye displays or touchscreen displays to boost active experience among older adults [85,100,119]. Some of the other tablets included iPads or television sets for software-driven visual interfaces or stimulation, such as creating self-portraits or life stories for older adults [52,58-60,81,87,92,93,96,109,121,131]. The tablets were used to connect residents with friends and family [72,105]. Some researchers delivered musical interventions using devices familiar to older adults, including the radio or MP3 players [45,57,66,87,99,120,131-134].

Outcomes of Interest

The majority of the articles reported positive outcomes (64/92, 69.5%), while a smaller portion had mixed results (28/92, 30%). Table S6 in Multimedia Appendix 7 outlines the measurement of the outcomes, and results. Positive outcome studies generally relied on descriptions of participant experience, such as analysis of interview conversations [50,59,91,135,136], questionnaires [53,78,81,100] and observations [48,49,54,66,68,72,85,97,102,115]. Studies with mixed outcomes tended to rely on the use of measurement tools like physiological tests [87] and observation [47,51,82,94,96,103,124,126,129]. In this context, positive/neutral/negative outcomes refer to the effectiveness and acceptability of the intervention among participants, reflecting both favorable and unfavorable responses.

Mood and Overall Well-Being

In total, 50 articles explored mood and overall well-being (50/94, 53%) [24,28,46-49,51,55,57,61,64,66-68,70,71,74,76,80-82,84,86,87,89,95,96,98,100-102,106-112,114-116,118,119,123,124,126,129,132,137,138]. Platforms such as computers and tablets [87,96,100,119] that helped to deliver virtual reality [115,116,118], exergames [28,74,123], and robotic companions [66,70,71,84,98] overall led to an improvement in mood and overall well-being, including feelings of gratitude [128] and behavioral symptoms of dementia [67]. Mood improvement was primarily measured via techniques such as surveys and questionnaires [46,47,81,98,100,108,112,123] including physiological assessment questionnaires [87] such as the UCLA loneliness scale or Geriatric Depression scale [80]. Improvements in mood were caused by either one or a combination of the following technology-enabled activities: socializing [49,91], music and dance [45,48,49,55,59,61,64,67,76,85,114,129,132], video or audio (nonmusic) entertainment [47,57,101], and art [24,81,124]. Where companionship was a targeted outcome, engagement with technology-enabled activities boosted feelings of excitement and belonging while also decreased feelings of depression, anxiety, and loneliness [80,107,108]. For example, robots or online pets facilitated companionship [101,108]. Online companions were largely pets that provided comfort to older adults that increased mood by allowing them to cuddle, play, or pet them [82,86,106,107,109,110], or watching, touching, or caring for the robot [71,101,138]. One study, however, found an increase in anxiety in individuals with mild cognitive impairment when using robotic pets as companions [101], which was contrary to an intervention which used music [76]. Games and activities with satisfying achievements for completion encouraged high self-esteem and validation among participants, especially when the challenges matched their cognitive abilities [28,61,95,119,125,126] or allowed autonomous art creation or viewing [24,51,124]. Another study which used a mobile-reminiscing therapy app found no change in mood [111].

Cognitive Health

A total of 19 articles (19/94, 20%) explored improvements to cognition facilitated through the use of exergames, tablet and computer applications, and robots or music, which provided stimulation [45-47,52,54-57,59,69,75,81,85,114,121,123,131,132,139]. Technologies that engaged participants in physical activity led to an outcome of improved cognitive health (although this was not defined) as such leisure activities stimulated motor skills often used in athletics [46,54,56]. Exergames were found to increase activity, only if the individual had sufficient cognitive ability (eg, having mild dementia vs severe) [123]. This was measured by a combination of usability testing processes and semistructured interviews [46], or observation combined with field notes ([54,54]. Opportunities to facilitate memories, often facilitated through videos, photos, and music encouraged expressive community engagement and relationship-building through shared experiences [45,47,52,55,57,59,75,85,132,139], provided beneficial cognitive stimuli that helped with conversation, which in turn was believed to be an indicator of improved cognitive health [81,121,131].

Functional Activity

Five articles (5/94, 5%) explored improvements to functioning in daily life. These were facilitated through exercising (via exergames [73,78]), robotic stimulation, and general time management and behavioral strategies [57,73,98,112]. One study classified improved functioning according to the World Health Organization's International Classification of Functioning, Disability and Health [70]. One study found that improved functioning included being able to maintain a schedule [98] and reduce fidgeting [57]. The studies found negative, or no improvement to sleep [57] and memory [93]. There are contrary findings around physical activity through exergames, with 2 studies suggesting negative or no improvement [73,131], and 1 study found that virtual reality cycling improved physical activity [122].

Discussion

The use of technology to deliver recreation and leisure activities for people living with impaired cognition is becoming more commonplace [11-15]. This rapid scoping review identifies and describes the existing literature that describes technologies used in recreation and leisure programs or activities that are delivered to older adults living with cognitive impairment. Our review found a diverse range of activities for older adults with cognitive impairment aged 50 [85] to 104 [86] years old, related to (1) socializing, (2) relaxation and self-awareness, (3) music and dance, (4) exergaming, (5) video or audio (nonmusic) entertainment, (6) playing games, and (7) art. Numerous technologies supported these activities and programs including the use of tablets [24,49-51,58,60,72,75,83,85,100,101,105,114,116,119,124-128], televisions [47,49,52,58-60,62,64,68,73,81,87,88,92,93,96,111,120,121,131], radio and MP3 players [45,57,66,87,99,120,131,132,134] or computers [6,7,61,87,90-92,94,95,98,115,116,129,130]. Touchscreen displays were frequently used to engage older adults in their activities [85,100,119], and some incorporated the use of artificial intelligence [48,49,80]. The technologies focused on obtaining various outcomes, including improving mood [24,28,46-49,51,55,57,61,64,66-68,70,71,74,76,80-82,84,86,87,89,95,96,98,100-102,106-112,114-116,118,119,123,124,126,129,132,137,138] and cognitive stimulation [45-47,52,54-57,59,69,75,81,85,114,121,123,131,132,139]. Many of the included studies reported positive results, supporting the use and effectiveness of some technologies to support recreation and leisure activities. However, study results should be interpreted within the context of their small sample size [56,71,84,92,99-101,107,111,128,131,134] and the lack of consideration for older adults with diverse cognitive and physical disabilities [71,74,84,100].

Technology-Related Challenges Within the Context of Recreation and Leisure Activities for Older Adults Living With Cognitive Impairment

Across the articles, authors raised numerous concerns about the use of technology to facilitate recreation and leisure activities for older adults with cognitive impairment. For instance, authors cautioned that technologies that focus on social interactions are not replacements for human companionship [98,100]. In the context of activities focused on reminiscing, some studies found that older adults may experience distress while observing photographs of deceased family members [99]. Technologies that use multimodal interactions (ie, verbal and visual) may be challenging and confusing for some people living with advanced stages of dementia [49,113]. Likewise, older adults' interest in, and acceptance of Wii and exergames games varied based on their cognitive health; people living with severe dementia were more likely to reject the games; whereas people living with mild dementia enjoyed exergaming but still needed supervision [123]. However, exergaming may not be cost-effective compared to usual treatment [78].

With reminiscence therapy, the process of obtaining relevant artifacts was time-consuming, and required commitment from family members [83]. The use of gaming systems for older adults also raised technical and ethical concerns for some scholars [92,125], as they may perpetuate low self-esteem, insecurity, and annoyance due to a lack of familiarity with the technology and lack of digital literacy [125,126]. Lastly, radios may experience reception issues (eg, static, signal dropping out) that can bother the participants [134]. Beyond the challenges with the technology itself, some studies reported that the technology was expensive, which may present a barrier to wide-spread implementation [78,82,84,109,138].

Many interventions discussed in this review, relied on costly robots, such as PARO [82,86,102,106,109,110], MARIO [99,103,113], and pet companions [101]. While pet companions increase older adults' mood, and robots allow them to care for these robotic pets which in turn increases their enjoyment, robot pets can also cause anxiety in individuals with mild cognitive impairment [101]. These results suggest the need for future research using similar interventions and may provide ideas for testable hypotheses to further investigate the benefits of using robots, including the target population and optimal timing during the illness trajectory. In comparison to tablets, robots can be prohibitively expensive for many older adults and care settings [140-142]. However, robots can often be customized to older

adults' preferences [143,144] unlike other off-the-shelf technologies, and thus might provide broader assistance in their daily lives and overall quality of life. Exploring options to adapt or customize lower-cost technologies like tablets to older adults' preferences may support wider adoption. Moreover, future studies are encouraged to provide more detailed information on how customizations occurred, and the development process for novel technologies. Engaging older adults with cognitive impairments and other stakeholders, such as care partners and health care providers, through a co-design design approach could add value when developing new technologies to support appropriate leisure and recreational activities. This approach helps researchers and technology developers gain in-depth insights into the preferences of different targeted populations [145-147].

Facilitators to Using Technology Within the Context of Recreation and Leisure Activities for Older Adults Living With Cognitive Impairment

Although there were some challenges with the technologies, many studies identified facilitators to their use across a variety of settings, such as having technical support easily accessible to older adults who were not familiar with technology [50]. In addition, hosting the technology in friendly spaces (eg, supportive environment, praise, and freedom to ask questions) helped older adults feel welcome to learn about new technologies [100]. A study found that the technical skills for gaming activities such as Nintendo Wii were learned, retained, and transferred to other leisure activities [54]. The availability of both technical support and emotional support is critical for older people who may not be as comfortable with the technologies as younger people [100]. Moreover, it is important for trainers to know how to communicate with and teach new skills to people living with dementia [28]. For example, certain types of prompts such as verbal prompts might not work well with some older adults [28]. Therefore, trainers must be capable and have a broad range of knowledge translation experience and problem-solving abilities so that people living with dementia will be optimally positioned to learn these new skills [28]. The use of animation and video might also make training processes more effective [81].

One study used robots that included infrared cameras that sent alerts to caregivers and nursing stations in case of emergency, and reminders for scheduled activities [112]. Robots with humanlike characteristics, including variable expressions, helped to engage older adults in recreational activities [108].

Researchers also found that older adults with mild cognitive impairment engage more in computer-based applications if they are provided in a gamified environment [50]. Computer systems with wheels were convenient for residents living in LTC homes as they could be transported from one room to another [92]. One system included a computer, webcam, microphone, speakers, hand or foot pedal for exercise and therapy, joystick, headset, and adjustable height unit for residents to allow play when standing or sitting [92]. Other computer systems could be set up using the existing television in resident rooms [121]. When feasible, setting up a new telephone line specifically for technology can help overcome connectivity and reception issues [134]. It is important to note that when computer activities match the interests and cognitive abilities of residents living with dementia in LTC homes, there is an increase in participation and satisfaction [61]. Verbal encouragement from LTC staff can also facilitate the use of technology [45]. Additionally, technology can help support staff deliver reminiscence therapy without additional training [111].

Few studies in our review reported information about participant ethnicity and comorbid conditions. Studies have shown that the digital divide (ie, the gap between those who have access, knowledge and use of technology, and those who do not [148]) is most pronounced for some racial and ethnic groups [149-151] and older adults [152]. Relying on technology to facilitate connection and belonging, and socialization and enjoyment between residents or with their families, may, therefore, exacerbate existing disparities in the well-being of older adults [153]. To address these disparities and promote inclusivity, research should explore the experiences of diverse older adults when using technology to support social and recreational leisure activities. Other barriers to be overcome include cognition [154], physical ability [154], low research literacy [155], lack of cultural competency [155], and speech- and language barriers [154,155]. These barriers occur in dementia research more broadly and have led to the underrepresentation of certain groups in research [155], limiting the generalizability of existing research.

To overcome these barriers, collaboration with community partners can be instrumental in ensuring inclusive recruitment and data collection strategies [154,156]. Such efforts can increase the representativeness of research samples and improve the translation of research findings to diverse populations and settings, into more effective and equitable technology interventions for engaging older adults in social and recreational leisure activities.

Methodological Recommendations for Researchers

The following 3 recommendations for scientists conducting research in this domain emerged from our analysis of the included articles:

1. Conduct research across settings: Most studies focused on a single setting, but it is suggested that research should be conducted in multiple settings such as home, community care, and health care institutions, because outcomes may vary due to the specific characteristics of each setting [45,99,115]. In addition, including individuals at various stages of cognitive impairment is crucial, as outcomes may vary between early-stage and advanced cognitive impairment [47,115,116]. In fact, few studies recommend prioritizing people with more advanced stages (moderate to severe) of cognitive impairment since there are severe challenges in managing symptoms and improving quality of life [106,115,116].
2. Increase the sample size and representation: Authors emphasized the need to increase sample size, which would allow greater demographic diversity in the research of older adults using technology for leisure and recreation [56,71,84,92,99-101,107,111,128,131,134]. This would include people with various types of disabilities

[71,74,84,100], and a greater number of male participants to gain a better understanding of gender in technology adoption [75]. Furthermore, some scholars have argued for an increase in caregiver samples to help explore how technologies could support them in their caregiving duties and help alleviate their stress, which is often overlooked within existing research [59,100,118].

3. Increase the use of experimental study design: Many studies recommended the use of different research methods, particularly experimental designs that use a control group to understand potential confounding factors [46,82,86,92,99,101,104,129,132]. This will help address questions about the validity of clinical outcomes [101,132]. Additionally, obtaining time series data on adoption and efficacy of technology will also help obtain deeper insights [46,56,57,96,108,118].

This review demonstrates that many existing technologies can support the socialization, relaxation, self-awareness and meaningful recreation and leisure activities of older adults, including playing games and creating art. Existing research has highlighted that engaging older adults living with dementia in meaningful activities can improve their quality of life [157-159]. An existing review explored the use of technology to promote engagement in adults with dementia living in residential aged care [159], whereas another explored technological interventions such as robots, tablets, and computers in the context of loneliness among individuals with dementia [15]. Our review expands on this existing knowledge by incorporating the diverse settings in which older adults engage in social activities, including hospices and community settings. However, a previous review noted that the benefits of engagement are not caused by the technologies themselves but rather in the opportunities the technologies provided to facilitate connection and belonging [159]. Therefore, more research is needed to understand the impact and benefits of technologies to facilitate connection and belonging, in comparison to standard care. Thus, a critical lesson from this review is the need to explore the existing barriers to connection and belonging, as well as the unique functions that technology can provide compared to those that can be provided by individuals such as formal and informal care partners.

In summary, our review confirms the growing interest among researchers in integrating technology into recreational and leisure activities for older adults, with most articles being published in the last 7 years. However, while there is interest in using technologies, there is a lack of large-scale, experimental studies, over time. Several factors may contribute to the limited experimental research in this area including the upfront costs of technology for older adults [160], older adults' training needs [161], and concerns regarding the long-term sustainability of these technology-enabled programs [162,163]. Implementation research is crucial to the scalability of technologies that might support adoption and sustainability [164,165]; its scarcity is notable in the existing body of literature. Additionally, the literature rarely described technologies being used across multiple care settings or the progression of diseases or conditions. Future research with different stages and settings will provide more insight into the diverse perspectives and values that participants bring when considering leisure activities [51].

Limitations

This study had several limitations. First, we only included English-language literature and excluded gray literature and conference abstracts, which may present preliminary findings. Consequently, it is possible that relevant literature was not captured by our search. Lastly, while we ran comprehensive electronic searches and adhered to an established methodology [40], the nature of a rapid scoping review including only 1-screener may have resulted in missed articles.

Conclusions

Technology has continued to emerge as a way to help engage older adults living with dementia in social and recreational leisure activities. Despite the availability of various digital technologies and their evaluation studies in the context of older adults, the literature is very sparse regarding how and how well they are developed, adopted, sustained, and evaluated. Current studies focus on the use of tablets, robots, televisions, computers, exergames, and radios, but little is known about the acceptability and feasibility of them in diverse settings, or about their clinical effectiveness. Moreover, included articles lack discussion on the adaptation of these technologies for older adults living with cognitive impairment and various forms of disabilities. Future research should take a more inclusive approach, incorporating design and development (ie, co-design approaches), testing, and implementation of technologies in diverse settings including home, community care, and health care institutions, and include a more diverse sample of older adults. By considering the specific needs and challenges faced by older adults living with cognitive impairment and other types of disabilities, researchers can develop technology-enabled recreation and leisure activities that are better suited to their unique requirements and promote their effective use in different contexts.

Data Availability

The data sets used in this study are available upon request. Access to these data sets can be requested by contacting KK at kristina.kokorelias@sinaihealth.ca. While not publicly accessible, all reasonable requests for data will be considered in compliance with our institutional policies and regulatory obligations.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA checklist.
[DOCX File , 35 KB - neuro_v3i1e53038_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOC File , 176 KB - neuro_v3i1e53038_app2.doc]

Multimedia Appendix 3
Characteristics of included peer-reviewed studies.
[DOCX File , 104 KB - neuro_v3i1e53038_app3.docx]

Multimedia Appendix 4
Target and actual sample.
[DOCX File , 109 KB - neuro_v3i1e53038_app4.docx]

Multimedia Appendix 5
Types of activities.
[DOCX File , 67 KB - neuro_v3i1e53038_app5.docx]

Multimedia Appendix 6
Creation of technology.
[DOCX File , 28 KB - neuro_v3i1e53038_app6.docx]

Multimedia Appendix 7
Study outcomes and measurements.
[DOCX File , 54 KB - neuro_v3i1e53038_app7.docx]

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Abbreviations

DIT: Dementia Isolation Toolkit
LTC: long-term care
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Viewpoint

Beyond Audio-Video Telehealth: Perspective on the Current State and Future Directions of Digital Neurological Care in the United States

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Abstract

Background: The COVID-19 pandemic transformed neurological care by both requiring digital health modalities to reach patients and profoundly lowering barriers to digital health adoption. This combination of factors has given rise to a distinctive, emerging care model in neurology characterized by new technologies, care arrangements, and uncertainties. As the pandemic transitions to an endemic, there is a need to characterize the current and future states of this unique period in neurology.

Objective: We sought to describe the current state of the pandemic- and postpandemic-related changes in neurological care and offer a view of the possible future directions of the field.

Methods: We reviewed several themes across the "new digital normal" in neurology, including trends in technology adoption, barriers to technology access, newly available telehealth services, unresolved questions, and an outlook on the future of digital neurology.

Results: In this new era of neurological care, we emphasize that synchronous audio-video telehealth remains the predominant form of digital interaction between neurologists and patients, mainly due to pandemic-related regulatory changes and the preexisting, steady adoption of video platforms in the prepandemic era. We also identify a persistent digital divide, with audio-only telehealth remaining a necessity for preserving care access. Asynchronous telehealth methods and services, including care coordination, interprofessional consultations, remote patient monitoring, and teletreatment are becoming increasingly important for neurological care. Finally, we identify several unanswered questions regarding the future of this "new normal," including the lasting effects of emergency regulatory changes, the value proposition of telehealth, the future of telehealth reimbursement in neurology, as well as privacy considerations and trade-offs in asynchronous neurological care models.

Conclusions: The COVID-19 pandemic has ushered in an era of digital adoption and innovation in neurological care, characterized by novel care models, services, and technologies, as well as numerous unresolved questions regarding the future.

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KEYWORDS

asynchronous telehealth; chronic condition management; COVID-19; digital health; digital neurology; eConsult; endemic; interprofessional consultation; neurological apps; neurological care; neurology; principal care management; remote patient monitoring; technology; telehealth legislation; telehealth; teleneurology

Introduction

The COVID-19 public health emergency significantly accelerated the adoption of digital technology in neurological care [1] and established synchronous and asynchronous telehealth as widely accepted care modalities across multiple subspecialties of neurology [2-7]. While historic, this acceleration also built upon the momentum generated by 2 decades of growing digital technology and service adoption in neurology. This momentum included the advent of telestroke [8], the establishment of video telehealth care programs in rural areas of the United States [9], and the growing use of smartphones and wearable devices in neurological care paradigms and research [10]. Furthermore, broad telehealth trends that led up to the COVID-19 pandemic, such as the shift of telehealth from acute to chronic neurological conditions, migration of care toward mobile device platforms, and increasing focus on patient convenience and value [11], also likely facilitated the shift to digital and web-based neurological care in 2020.

Approximately 3 years after the start of the COVID-19 pandemic in the United States, the field of neurology has transitioned to a new digital environment, encompassing new and emerging care models and services, novel technologies, as well as new and persistent challenges and open questions. While this new digital landscape is wide-ranging, complex, and often subject to rapid changes, a comprehensive appraisal of the current state of care can nonetheless be helpful in establishing policy priorities and identifying opportunities to improve access to digital technologies for patients with neurological conditions. In this review, we sought to describe the digital state of neurology care in the COVID-19 and post–COVID-19 eras, placing emphasis on dominant forms of digital neurological care, emerging technology trends and technology-enabled digital neurology services, barriers to access to digital care, telehealth in education, as well as ongoing challenges and uncertainties facing the future.

Themes

Video Telehealth Is the New Dominant Digital Care Modality

Comparisons Between Pre–COVID-19 and Late Pandemic Use

The COVID-19 era saw synchronous audio-video (or simply "video") telehealth fundamentally shift away from a novelty technology garnering little interest among most practicing neurologists to an acceptable alternative to in-person face-to-face encounters and other traditional neurological care modalities for patients and providers [12]. In late 2021, the use of video telehealth in multiple medical specialties remained approximately 38 times higher in the United States than before the onset of the pandemic and comprised 13% of neurology outpatient visit claims nationwide [13]. On the health system level, the use may be even higher, with certain rural health systems recently noting that nearly 35% of ambulatory neurology visits were conducted through telehealth. For many neurologists nationwide, synchronous video telehealth remains the preferred mode of telehealth delivery, followed by audio-only telehealth [14]. Compared to the relatively infrequent use of video telehealth in neurology before 2020, these findings all underline the important place video telehealth now occupies in modern neurological care.

Factors Driving the Rise and Predominance of Video

Insurance payment incentives were important in driving video telehealth's initial rise to prominence in neurology during the pandemic, especially in the United States. In declaring the COVID-19 public health emergency, the Centers for Medicare and Medicaid Services (CMS), the nation's largest insurance payor, suspended multiple geographic restrictions for video telehealth insurance reimbursement that had previously limited patients from being evaluated over video telehealth in their homes and outside of designated rural areas, effectively limiting uptake and contributing to the "novelty" status of video telehealth before the pandemic [15]. The lifting of such restrictions early on in the pandemic and their continuing suspension in later stages of the pandemic have incentivized patients, providers, practices, and health care systems to widely use video telehealth.

Additional factors that have contributed to the continued dominance of video telehealth in neurology include high and steadily increasing rates of smartphone ownership across the world [16] and the liberal allowance of several platforms for telehealth, particularly in the United States. More specifically, enforcement discretion of HIPAA (Health Insurance Portability Accountability Act) regulations by the US Department of Health and Human Services during the public health emergency allowed non–HIPAA-compliant technology platforms to be widely used for video telehealth purposes [17].

Patients and neurologists have reported positive experiences with video telehealth, which have likely preserved telehealth's dominance as a digital offering in our current era. Video telehealth is perceived as convenient [18,19] and rated as highly satisfactory among patients [2,20]. Similarly, notwithstanding some reports suggesting that providers have had greater challenges than patients with video telehealth encounters [2], neurologists have generally found satisfaction, positive experience [21,22], and effectiveness [23] with video telehealth visits.

Elements of the Neurological Examination

Although the feasibility and accuracy of a detailed, video-based neurological examination have been the subject of debate among the neurological community, the pandemic era mandated the need for remote neurological examinations and accelerated the adoption of additional examination methodologies for performing the digital neurological examination beyond video technology. These phenomena build upon previous work demonstrating that video-based neurological examinations can accurately be used to administer standardized disease-specific examinations, such as the Unified Parkinson Disease Rating Scale (UPDRS) for Parkinson disease [24], the Unified Huntington Disease Rating Scale [25], or the Montreal Cognitive Assessment in individuals with movement disorders [26].

Additional examples include digital versions of the Expanded Disability Severity Scale in multiple sclerosis [27], the Multiple Sclerosis Performance Test [28], or the Myasthenia Gravis TeleScore [29].

While recent work has suggested not only that many elements of the neurological examination could be completed over video telehealth, additional studies have suggested that patients themselves may be assessed through functional evaluation (eg, performing exercises or shifting from sitting to standing position), serve as their own examiners, as well as use household items such as flashlights, toothpicks, or weights to aid neurological assessments [30,31]. More importantly, most elements that are most useful for neurological decision-making can be performed over a video connection [23].

Despite this, several elements of the neurological examination remain challenging to routinely perform over video telehealth, such as fundoscopy, vestibular testing, visual field examination, and muscle tone. Among these elements, televestibular and fundoscopy assessment technologies currently exist but typically require additional hardware beyond video-enabled smartphones, thereby creating persistent barriers to use for most patients and providers. Although these shortcomings do exist, they nonetheless represent fertile ground for future technological innovations to address the objective of completing entirely digital neurological examinations. Indeed, neurologist surveys suggest that devices to perform gait, sensory, fundoscopic, oculomotor, and strength assessments are highly desirable to complement the video examination [32].

Perceptions of the adequacy of the digital neurological examination may also vary according to subspecialty. In a recent survey of academic neurologists, neuromuscular specialists expressed dissatisfaction with performing the neurological examination over video, mainly due to an inability to assess reflexes and tone. By contrast, movement disorder specialists expressed concern over inadequate internet bandwidth for bradykinesia assessments as well as unwieldy camera angles that precluded in-depth evaluation of gait [33].

While these perceptions express some sense of dissatisfaction, they nonetheless reflect that different neurological subspecialties tend to emphasize different components of the neurological examination (and, by extension, the remote neurological examination) more than others. Accordingly, numerous subspecialty-oriented teleneurology examination guides have been developed since the onset of the COVID-19 pandemic, which are now available through multiple web sources, including professional society web pages [34].

These guides emphasize examination elements that differ according to subspecialty. For instance, neuromuscular examination guides suggest using validated scales such as the Myasthenia Gravis Activities of Daily Living or the Revised Amyotrophic Lateral Sclerosis Functional Rating scales, assessing upper extremity tone by holding the patient's arms out and shaking them to assess for rigidity, determining motor strength by observing limb movement against gravity, and evaluating plantar responses by asking the patient to stimulate the plantar surface of their feet with a pen [35]. By contrast, guides for neurovestibular or neuro-ophthalmic disorders tend to emphasize the oculomotor examination and vestibular or visual field testing [36].

Evidence Supporting Teleneurology

In the decade leading up to the COVID-19 pandemic, a multitude of studies had already investigated the quality impacts of specific teleneurology care, including user satisfaction and diagnostic accuracy, as well as impacts on clinical outcomes, costs, and care access across multiple neurological conditions encompassing dementia, multiple sclerosis, movement disorders, headache disorders, inpatient neurology, traumatic brain injury, neuromuscular disorders, and epilepsy (Table 1). Randomized controlled and inferiority trial evidence generally suggests that teleneurology is associated with positive impacts on clinical outcomes, diagnostic accuracy, and physician or patient satisfaction. Studies carried out in the post–COVID-19 era have demonstrated similar findings with respect to satisfaction [37]. Improvements in cost-savings and care access were noted in mainly small or nonrandomized studies, although there were notably absent studies suggesting the latter in dementia, headache, multiple sclerosis, and neuromuscular disorders (Table 1) [38].

At the time of writing, nearly 50 US institution–sponsored telehealth trials in prevalent neurological disorders, including Parkinson disease, stroke, multiple sclerosis, epilepsy, Alzheimer dementia, and headache disorders, are either active or currently recruiting participants. Although a small minority of these initiatives are not yet recruiting, these studies include both observational and interventional trials to evaluate a range of outcomes, including but not limited to feasibility, comparative effectiveness, cost-effectiveness, and safety measures (Multimedia Appendix 1).

Table 1. Summary of available data across multiple quality measures of teleneurology by specialty. The table represents extant evidence on telehealth in neurology as of early 2020. Reproduced with permission from Wolters Kluwer from Hatcher-Martin et al [38].

	Patient and physician satisfaction	Improved access to care	Diagnostic accuracy	Improved outcomes	Cost savings (patient and health system use)
Concussion or traumatic brain injury	+[a]	+	++[b]	++	+
Dementia	++	—[c]	++	+	+
Epilepsy	+	+	—	++	+
Headache	++	—	++	++	+
Movement disorders	++	+	++	++	+
Multiple sclerosis	++	—	++	++	+
Neuromuscular	++	—	—	+	+
Inpatient general neurology	—	+	+	+	+

[a]+: small case series, indirect measurement.

[b]++: randomized controlled trial or inferiority trial, direct measure.

[c]No studies.

Factors Limiting Digital Neurology Uptake

Persistent, Widespread Disparities and Barriers

Several digital and socioeconomic inequalities in the US health care system clearly preceded the COVID-19 crisis that persisted throughout the early and late phases of the pandemic and profoundly impacted the adoption of digital care modalities during the public health emergency. Indeed, telehealth was less readily adopted among low-income, minority, non–English-speaking, and governmentally insured neurological populations during the early and middle stages of the pandemic [4,39,40], and access to audio-video telehealth has continued to demonstrate limited uptake among Black and governmentally insured populations in later pandemic stages [41].

Defined as "the gap existing between individuals who have access to modern information and communication technology and those who lack access" [42], the "digital divide" has been cited as a primary driving factor for asymmetrical digital neurology service adoption in the COVID-19 era. This perception has also persisted among providers. More than 2 years after the beginning of the COVID-19 pandemic, this "digital divide" continues to serve as the largest barrier to offering telehealth services among US providers [14]. Possible causes driving these asymmetries may include digital literacy, a lack of non–English-language interfaces, the prohibitive economics of steady digital access, limited access to broadband internet, inadequate cellular data plan coverages, and potentially cultural factors.

It remains important to note that many of the disparities that have been observed in the uptake of telehealth in neurology are not unique to digitally enabled care platforms. Rather, they tend to closely mirror existing sociodemographic disparities in access to neurological care that have been long observed in "nontelehealth" neurological care. Indeed, socioecological factors have been identified by numerous stakeholders as driving the vast majority of health disparities in neurological care [43]. Analyses of specific neurological conditions also reflect sociodemographic disparities in care. For example, Black and Hispanic patients are less likely to see outpatient neurologists across a range of neurological disorders, including headache disorders, Parkinson disease, stroke, and epilepsy [44]. Similarly, Black patients have lower odds of receiving thrombolytic therapy for acute ischemic stroke nationwide than White patients. Rural patients have similarly decreased odds compared to urban patients, as do patients living in ZIP codes with median incomes under US $64,000 in comparison to those living in wealthier ZIP codes [45]. A number of additional analyses have emphasized racial or sex-based disparities in multiple neurological disorders and treatments, including deep brain stimulation and general treatment for Parkinson disease, temporal lobe resection for medication-refractory epilepsy, evaluation and management of neuro-oncologic conditions, and treatment of acute stroke [46-51].

The Critical Importance of Audio-Only Telehealth

In light of the digital divide and asymmetric digital neurology adoption, audio-only services remain centrally important to the new digital normal in neurology. Synchronous, audio-only telehealth has played an important role as an alternative to synchronous audio-visual telehealth since the outset of the COVID-19 pandemic in 2020. This role has persisted through multiple phases of the pandemic, particularly for populations lacking regular access to broadband internet and cellular data connectivity, including older people, disabled people, or socially disadvantaged groups among both nonneurological [52,53] and neurological populations [39,40,54].

Although single-center evidence suggests that usage of telephone services may have steadily decreased in academic centers in later stages of the pandemic [55], a primary driving force toward use of audio-only telehealth services throughout the pandemic was CMS' decision in March 2020 to temporarily add American Medical Association (AMA) Current Procedural Terminology (CPT) telephone-only evaluation and management billing codes to a list of billable telehealth services for the duration of the public health emergency [15].

Several factors underscore the important role of audio-only telehealth currently plays and will likely continue to play in

care delivery during the pandemic era and beyond. At the time of writing, the US government has upheld the declaration of the COVID-19 public health emergency, thereby guaranteeing that telephone services will continue to be treated as billable telehealth services through the calendar year 2023. Furthermore, audio-only services continue to provide a crucial access point to health care. Indeed, a significant proportion of providers continue to use audio-only telehealth, with many reporting this to be second only to synchronous audio-video telehealth [14]. Recognizing the importance of audio-only telehealth, professional societies such as the American Academy of Neurology have called on CMS and the US Congress to make reimbursement rates for audio-only services permanent after the cessation of the federally declared COVID-19 public health emergency.

The Increasing Importance of Asynchronous Telehealth

Asynchronous Teleneurology

Synchronous telehealth currently occupies a central position in the universe of today's available complement of digital neurology services. By comparison, asynchronous telehealth, in which geographically disparate participants are separated by time as well as location, remains poorly used. However, it is important to the growing importance of asynchronous telehealth as part of the "new digital normal" in neurology. At the most basic level, this form of telehealth includes well-established modes of digital communication, such as email and SMS text message, but can range to more complex technological implementations. From a functional perspective, asynchronous telehealth in neurology can be organized into 4 general categories: remote diagnostic services (telemonitoring), remote delivery of neurological treatments (teletreatment) [56], electronic interprofessional consultations, and care coordination.

The pandemic era has seen a number of new billable clinical activities emerge in the United States that have facilitated the rising importance of asynchronous care services in neurology. These services include remote patient (also termed "physiologic") and therapeutic monitoring, digital check-ins, digital evaluation and management, principal care management (PCM), and interprofessional consultations. In addition to these billable services, these activities also substantiate a growing trend in digital neurology in which centralized, inconvenient, and synchronous care models are progressively shifting toward distributed, asynchronous models that prioritize patient convenience and access [10]. The onset of the COVID-19 pandemic in early 2020 accelerated this shift by expanding the adoption of asynchronous services as well as synchronous ones [57,58].

Telemonitoring

Neurological telemonitoring now encompasses a wide range of clinical services. A commonly encountered form of telemonitoring includes smartphone apps or electronic health record (EHR) questionnaires that receive patient-centered symptoms, validated clinical scales, or medication compliance information that is then transmitted electronically to a care team with the purpose of establishing a diagnosis or monitoring responses to treatment [59]. Examples of such apps abound in neurology, which comprises many chronic, polyphasic disorders such as migraine [60-62], multiple sclerosis [63,64], epilepsy [65], and Parkinson disease [66], among others.

Telemonitoring also includes "store and forward" services, in which a patient transmits clinical image information such as digital image, recorded audio, or video to a treating provider team for asynchronous review. A particularly useful application of store-and-forward in neurology is the diagnosis of paroxysmal neurological events, such as seizure-like episodes [67], as well as a close review of dynamic neurological examination findings in Parkinson disease [68-70].

Remote patient monitoring (RPM), an already well-established form of telemonitoring in nonneurological conditions such as congestive heart failure, chronic obstructive pulmonary disease, and diabetes, occupies an increasingly important position in the care delivery to patients with neurological disorders. Similar to nonneurological applications, neurological RPM uses sensor-containing patient wearable devices, occasionally paired with mobile app platforms, to record and transmit continuous or near-continuous physiological information to care providers for review and medical decision-making over a secure internet connection [71]. In neurology specifically, the growing importance of telemonitoring capitalizes on the growing understanding that episodic patient assessments often provide incomplete and sometimes inaccurate assessments of patients' clinical and functional status [10].

However, neurological RPM notably differs in data acquisition and transformation techniques from its nonneurological counterpart. Because most neurological disorders rely on a combination of qualitative radiographic or clinical examination findings to establish a diagnosis or inform management rather than laboratory or vital sign information, neurological RPM generally uses raw data from limb accelerometer and gyroscope sensors to extrapolate meaningful "digital biomarkers" such as gait, arm swing, step count, falls, examination findings, or abnormal movements. This is in contrast to nonneurological RPM, where sensors directly measure clinically relevant biomarkers such as blood pressure, blood glucose, or oxygen saturation, for example [72,73].

Notable areas of RPM application to neurology include disorders with prominent motor and gait features such as multiple sclerosis [74] and movement disorders [75-78]. In addition to demonstrating feasibility and acceptability, RPM has potentially identified novel digital biomarkers. One notable example is the daily step count, which is associated with functional status decline in patients with multiple sclerosis [74] and incident dementia [79]. While these RPM approaches are not yet established as standard-of-care, they are being used increasingly in clinical and research applications with an understanding that further work is required to better grasp the implications of collecting and transmitting this information [56].

Important to note are the few instances of fully integrated, scaled neurology RPM programs in health care systems in the United States as well as the relatively underused nature of these services by neurologists. Nationwide analyses of US Medicare claims data suggest that neurologists comprise a very small proportion

of RPM-billing providers [80,81]. Interestingly, analysis of nationwide commercial claims data shows that only 14% of the nearly 17,000 RPM encounters billed by physicians to commercial payers for neurological disorders between 2019 and 2021 were billed by neurologists, compared to 57% that were billed by family medicine, pulmonary, and internal medicine providers combined. Moreover, nearly 90% of these encounters were billed for sleep-wake disorders, with approximately 2% billed for common neurological conditions such as cerebrovascular disorders, movement disorders, epilepsy, migraine disorders, and polyneuropathies combined (B Kummer et al, unpublished data, 2023). These data suggest that despite its promise, RPM is underused by neurologists for neurological conditions, particularly those that constitute relatively straightforward clinical use cases, such as blood pressure monitoring after stroke, or step counting in multiple sclerosis, movement disorders, or neuropathies.

While billing activity reflects a limited dimension of RPM use, the reasons for these findings could be that few Food and Drug Administration–approved devices (a requirement for billing new RPM codes issued after 2019) for monitoring physiologic signals in neurological conditions currently exist. Alternatively, high variability in the quality and availability of commercial wearables and sensors may explain RPM underuse by neurologists. Finally, the lack of integration of many RPM solutions into EHR systems is likely a contributing factor that has been identified as an important barrier to the adoption of RPM services into real-world clinical settings across a spectrum of medical specialties [82].

Teletreatment

Neurological teletreatment is now widely available for the management of headache, epilepsy, and movement disorders. A notable category of teletreatment options comprises stimulator devices that deliver focused electricity to selected nervous system regions [83], including vagal nerve stimulators, responsive neurostimulators, and deep brain stimulators, which have all found application in epileptic [84] and movement disorders [85]. In migraine and other headache disorders, analogous devices include peripheral stimulator devices targeting the supraorbital, occipital, or sphenopalatine ganglion [86]. Many of these devices can be remotely programmed by a provider as well as collect and relay neurophysiologic data back to care teams for treatment decisions. Furthermore, device programming parameters can potentially be integrated into EHR systems to provide a snapshot of the patient's clinical status.

Some authors consider technology, per se, to constitute treatment [87] and therefore represent an additional subcategory of teletreatment. Under this conceptual framework, mobile health apps that are capable of various monitoring and diary functions may be thought of as treatment in and of themselves. One notable application of "technology as treatment" includes headache disorders, where symptom diaries may provide insight into disease processes and inform treatment or guide complementary and integrative therapies that modulate stress levels and pain perception [59].

Care Coordination

In response to the rising prevalence of chronic conditions and their significant associated costs in the United States, CMS has developed billable care management and coordination services in the second decade of the 21st century that make extensive use of asynchronous telehealth interactions and represent another increasingly important example of asynchronous teleneurology in the COVID-19 era. These services are best exemplified by chronic care management (CCM; introduced in 2015), which supports care management of multiple chronic conditions, and PCM (introduced in 2022) for the management of a single complex condition. These services incentivize an integrated, team-based approach to chronic condition management by bundling care coordination, care planning, and condition-focused goal setting into an overarching care management activity that is primarily furnished through non–face-to-face encounters. Both PCM and CCM allow care teams to interact with patients asynchronously, using the technology platform of their choice. Furthermore, CCM specifically includes care monitoring in the definition of billable service, thereby allowing the use of RPM and remote therapeutic monitoring.

In addition to CCM and PCM, coordination of care can be performed through asynchronous patient portal communications between patients and providers. These communications dramatically increased with the onset of the COVID-19 pandemic [88], potentially as a result of increased video telehealth adoption and the absence of office-based follow-up arrangements. In addition to care coordination, the potential for completing true evaluation and management of new medical problems over patient portals led to the introduction of new digital evaluation and management services (or "e-visits") in 2020 as billable codes (CPT codes 99421-99423 and Healthcare Common Procedure Coding System codes G2061-G2063). While several US health care institutions in the United States have successfully implemented billing for e-visits and increased the volume of these services [89], some of these implementations were accompanied by decreases in the use of portal messaging and suggested that few portal messages were truly billable as e-visits, arguing that these services have not lessened the cognitive overload imposed by significant increases in patient portal messaging [90,91].

Interprofessional Consultations

Although much of neurological telehealth refers to patient-provider interactions, consultations between providers remain an important area of digital care in neurology. Telephone calls between providers and synchronous video teleneurology consultations have existed for decades, with telestroke constituting perhaps the most widely known example of the latter [8]. Despite this, a growing number of interprofessional neurology consultations are now performed asynchronously and have been successfully implemented in headache and neuro-ophthalmic conditions, leveraging electronic forms of communication such as email, clinical notes, or direct verbal communication over the telephone to requesting providers [92-95]. Although discussion of recommendations with the requesting provider may be a synchronous interaction, the bulk of the service is provided asynchronously.

Aside from the application of interprofessional consultations to specific neurological conditions, some notable use cases for this emerging service include improving access to neurological expertise in the setting of worldwide neurologist shortages [93,96], limiting personal exposures to hospitalized patients with diseases carrying significant infectious risk such as COVID-19, or improving the ability to evaluate and manage common neurological problems among nonneurologists [95]. To incentivize this activity, in a manner similar to CCM and PCM, CMS has delineated billable interprofessional consultation services, for which a discrete number of acceptable billing codes have been developed [97].

The Future of Digital Neurology

The future of digital neurology can be organized into 3 broad areas: new information processing methods, new data types, and the provision of care through new modes of interaction. New processing methods are likely to include artificial intelligence (AI) processes that automate the detection of clinically meaningful information (assistive AI), analyze automatically collected information (augmentative AI), or analyze and draw independent conclusions from providers (autonomous AI) [98]. While assistive and augmentative AI is already in use within individual disease states, including stroke [99], Parkinson disease [68-70], or epilepsy [100,101], augmentative AI remains the least widely represented approach.

However, AI processes will probably not evolve to replace providers or medical decision-making but rather automate simple processes to allow providers greater bandwidth to tackle an increasingly complex array of neurological disorders [102].

In addition to the growing role of AI, multilayer synthesis, or "phenotyping," of complex data streams is likely to become more common as the use of physiological, structured EHR, textual, and other data streams grows in neurological disorders [103]. This phenotyping may be used to serve multiple objectives, including the automation of standardized clinical assessments in key disorders such as the National Institutes of Health Stroke Scale or the UPDRS, the characterization of clinically meaningful disorder manifestations or outcomes, or the identification of novel disease subpopulations.

The future of digital neurology will also likely entail the exchange of novel data types, including videos of neurological events, examinations, and phenomenology, with or without AI assistance, as well as social network activity and geo-localization data to quantify patient "digital life space." Treatment information, such as responses to individual therapies, adverse events, medication compliance, and symptom diaries, is likely to become increasingly common within the ongoing digitization of neurology. Additionally, as sensors become increasingly sophisticated and compact, RPM in neurological disorders will likely evolve to incorporate additional sensor streams such as magnetometry, skin galvanic responses, and other novel biomarkers into routine clinical care [103].

Finally, private companies and health system strategies' shift toward convenience- and patient-oriented care journeys is likely to impact the manner in which patients with neurological conditions and providers interact. Semi- or fully automated chatbots, which are already widely available in the retail and banking industries, may eventually provide around-the-clock access for simple questions that do not require high-level clinical decision-making. Recent private-sector initiatives featuring on-demand, search-engine–based and technology-forward health care for large populations of patients [104-106] suggest that such "digital front doors" may become the primary method of locating neurological expertise and obtaining resources for patients with neurological disorders, rather than relying on referrals from providers and other traditional pathways.

Unanswered Questions: a Look Toward the Future

The Telehealth Value Proposition

The value of telehealth and whether telehealth adequately attains desired health outcomes relative to the cost of care delivery [107,108], remains a largely open question across medical specialties. Although video telehealth is associated with significant patient and provider benefits, it has been shown to generally increase costs, with the exception of cases of eliminating long-distance travel [109]. More recently, a study investigating the value of telehealth in young adults with cancer overwhelmingly found that telehealth resulted in cost savings [110].

In contrast to the limited investigations of value in nonneurological conditions, modern telehealth for neurological care faces an uncertain future with respect to the question of value. Although the question chiefly concerns synchronous audio-video telehealth, which is arguably the most common digital neurology interaction today, the telehealth value question remains relevant to all forms of digital neurological care [14]. Outside of synchronous telestroke care, which has long been one of the clearest examples of telehealth value in neurology before the COVID-19 pandemic era [111,112], there remains a dearth of information regarding whether synchronous telehealth provides an acceptable value of care in noncerebrovascular neurological conditions. Large-scale, multicenter studies should address this specific question for synchronous audio-video as well as asynchronous forms of telehealth as applied to neurological disorders [108].

Governmental or Public Health Emergency Restrictions: the Future of Telehealth Reimbursement

By facilitating the adoption of various digital neurology modalities among providers and patients, the suspension of multiple telehealth reimbursement restrictions due to the COVID-19 public health emergency by the US federal government figures among the principal driving forces in catalyzing the widespread use of digital neurology services during the pandemic era [1]. At the time of writing, the public health emergency officially ended on May 11, 2023 [113], after which many suspended restrictions, such as CMS reimbursement for video telehealth visits irrespective of geographic locations, were extended into the end of 2024 [114]. However, many exemptions, including temporary reimbursement of specific telehealth services as category 3 codes and flexibilities involving controlled substance prescription over telehealth, among others, were extended only until the end of 2023. The rapidly changing flexibility landscape as well as the multiplicity of time frames

create a complex matrix of different regulations that is often overwhelming and confusing to providers [115].

As opposed to federal-level restrictions, medical licensure and scope of practice continue to be regulated by individual US states, which restricts providers from delivering telehealth care to patients not located in states where the provider is licensed. To maximize patient access to telehealth care early in the COVID-19 pandemic, several US states loosened licensure requirements in order to allow out-of-state providers to easily obtain temporary licenses. However, since the end of the federal public health emergency, many states have rescinded these temporary flexibilities, with unclear impacts on telehealth use. It remains similarly unclear whether the Interstate Licensure Compact, an agreement signed by 37 US states and territories to simplify the licensure process for providers who wish to practice in multiple states [116], will positively impact the use of telehealth broadly speaking.

While the US Congress has introduced a bill to make several pandemic suspensions permanent [117], many specifics concerning the postpandemic regulatory landscape beyond 2024—and impacts on the long-term feasibility, viability, and adoption of digital modalities such as synchronous and asynchronous telehealth—remain unclear. As such, the rapidly approaching end of this extended period represents a significant source of uncertainty for the new digital normal.

Privacy Considerations of New Digital Interactions

Although privacy and security of personal health information for the purposes of medical care is strictly regulated by HIPAA in the United States, another important aspect of the new digital normal in neurology is the proliferation of digital technologies and services that collect and transmit personal health information but are not considered to be the provision of medical care or constitute a health care relationship under US federal law [118]. While this implies that they are not regulated under the purview of HIPAA, many of these technologies are nonetheless commonly used by providers and patients for the diagnosis and management of neurological conditions. Concerningly, mobile apps have been shown to disclose unauthorized personal health information outside of their end-user licensing agreements [119,120].

Patients using all forms of unregulated digital neurology services are therefore faced with a fundamental trade-off between collecting clinically meaningful information and infringing upon personal privacy. Sharing personal health information, even if knowingly, can potentially have undesired consequences. One particular venue in which this is evident is the growing phenomenon of employee wellness programs that collect physical activity and geospatial position information through wearable devices. These could disclose an employee's actions during work unbeknownst to the wearer and potentially result in disciplinary action.

Open questions remain as to which venue is appropriate for regulating these issues. At the time of writing, in the United States, CMS and billing stakeholders such as the AMA have not taken any official stance against limiting the sharing of personal information on asynchronous teleneurology platforms, with most controls existing at the level of specific company data use policies and end user licensing agreements at the level of user acceptance.

The Future of Digital Neurology

During the COVID-19 public health emergency, digital neurology modalities clearly ensured safe access to neurological care for patients, resulting in significantly increased adoption and awareness of these tools among patients and providers. Asymmetric adoption of digital tools across different populations also cooccurred during the rapid rise in adoption, exposing the significant, persistent challenge facing the US health care system: access to specialty care [121]. Despite this, digital care modalities continue to demonstrate beneficial effects on care access and value [110,122-124] and carry even greater potential for the future of the health care system.

The "new digital normal"—within and outside of neurology—will realize this potential by reaching 3 critical milestones. The first is to shift the current digital operating framework, which places a significant focus on the range of available digital care solutions and their technical differences (eg, audio-only or audio-video and asynchronous or synchronous), to a structure emphasizing a tailored approach to digital care that combines "doses" of different technical solutions to individualized patient use cases.

The second will be to incorporate the rapidly growing array of AI technologies as complementary solutions in the current armamentarium of technical options targeting care access bottlenecks. By accelerating diagnosis recognition, automating clinical processes, and reducing provider cognitive overload, AI can effectively accelerate access to neurological expertise throughout the health care system. As such, this emerging set of technological innovations will likely prove itself to be a crucial complement to currently available digital tools.

The third milestone is creating a sustainable reimbursement framework that incentivizes providers to use digital tools. Efforts targeting this milestone are already underway at the time of writing and include the development of coding structures targeting clinical activities centered on specific technical solutions as well as classifying machine-performed clinical work [98,125].

Conclusions

Contrasting with the temporary nature of the public health crisis itself, the COVID-19 pandemic has profoundly and indelibly altered the practice of neurology and medicine as a whole, ushering in an era of digital technology adoption and innovation characterized by novel care digital care models, services, and technologies. Despite the significant uncertainty and numerous unresolved questions facing this new digital normal in neurology, reverting to "prepandemic" technical solutions and care arrangements is failing to capitalize on one of the greatest opportunities to move medicine forward in the history of our species. It is crucial to consider the unprecedented scale and depth of digital health innovation that has occurred during this time [121] and the primordial importance of continued

innovation in order to bring neurology and all specialties of medicine into the next phase of this “new digital normal.”

Conflicts of Interest

NAB has received personal compensation for serving as an editorial advisory board member for Neurology Today, as a speaker for the American Academy of Neurology (AAN), and as the AAN’s primary advisor to the American Medical Association’s Current Procedure Terminology Editorial Panel. BRK has served as a consultant for Syapse, NeuraHealth, BrainKey, Gerson Lehrman Group, AlphaSights, Guidepoint Global, and Atheneum Partners; holds equity ownership for serving on the advisory board of Syntrillo; and has held speaking engagements with the American Medical Association and the American Academy of Neurology.

Multimedia Appendix 1
Summary of current (recruiting, active but not recruiting, and enrolling by invitation) US institution-sponsored clinical trials of telehealth in selected neurological disease that have launched since the start of the COVID19 pandemic in March 2020. Source: ClinicalTrials.gov; accessed December 7th, 2023.
[XLSX File (Microsoft Excel File), 31 KB - neuro_v3i1e46736_app1.xlsx]

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Abbreviations

AI: artificial intelligence
AMA: American Medical Association
CCM: chronic care management
CMS: Centers for Medicare and Medicaid Services
CPT: Current Procedural Terminology
EHR: electronic health record
HIPAA: Health Insurance Portability Accountability Act
PCM: principal care management
RPM: remote patient monitoring
UPDRS: Unified Parkinson Disease Rating Scale

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Viewpoint

Ethics and Governance of Neurotechnology in Africa: Lessons From AI

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Abstract

As a novel technology frontier, neurotechnology is revolutionizing our perceptions of the brain and nervous system. With growing private and public investments, a thriving ecosystem of direct-to-consumer neurotechnologies has also emerged. These technologies are increasingly being introduced in many parts of the world, including Africa. However, as the use of this technology expands, neuroethics and ethics of emerging technology scholars are bringing attention to the critical concerns it raises. These concerns are largely not new but are uniquely amplified by the novelty of technology. They include ethical and legal issues such as privacy, human rights, human identity, bias, autonomy, and safety, which are part of the artificial intelligence ethics discourse. Most importantly, there is an obvious lack of regulatory oversight and a dearth of literature on the consideration of contextual ethical principles in the design and application of neurotechnology in Africa. This paper highlights lessons African stakeholders need to learn from the ethics and governance of artificial intelligence to ensure the design of ethically responsible and socially acceptable neurotechnology in and for Africa.

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KEYWORDS

neurotechnology; Africa; AI; ethics; governance; ethics dumping; regulations; artificial intelligence

Introduction

The increasing convergence of neuroscience, engineering, materials science, and emerging technologies, such as artificial intelligence (AI), robotics, extended reality, and so on, has given rise to a novel technology frontier called neurotechnology. Once dismissed as the stuff of fiction, cutting-edge invasive and noninvasive neurotechnology is now becoming the reality of our time. Significantly intertwined with advancements in AI, machine learning, and deep learning, neurotechnology holds tremendous promise for research and practice. From brain imaging devices that have transformed our understanding of brain structures and functions to neuromodulation and neurostimulation devices that improve the quality of life of people with brain disorders, neurotechnology is revolutionizing our perceptions of the brain and nervous system. It is also becoming a booming industry with growing private and public investments in direct-to-consumer neurotechnologies [1]. This is owing to a number of factors, including the increasing prevalence of brain diseases and the increasing integration of innovation into biomedical research and practice.

In the last decade, many countries and regions have recognized the need for a maintained public investment in brain research as a priority. Some of the publicly funded large-scale brain research projects include the US Brain Initiative (US $3 billion), the EU Human Brain Project (€607 million), China Brain Project (US $746 million), Japan BRAIN/MINDS (US $365,163,41), Australian Brain Alliance (US $500 million), Canadian Brain Research Strategy (US $250.3 million), and Korea Brain Initiative (US $1.2 billion) [2]. These projects and the emerging landscape of public and private funding opportunities have created a global ecosystem where countries in Africa and other developing countries in the Global South are being left behind in brain research and innovation. Public funding for neuroscience research and innovation is almost nonexistent in Africa [3]. Neurotechnology research and innovation are practically being developed in select countries in North America, Europe, and Asia. These are tech devices that are currently being introduced in African contexts and to African consumers.

However, as it has been identified in other emerging technologies, such as AI, technology is developed with a specific context in mind and reflects the dynamics of that context. The use of the technology beyond the context it was created for raises concerns, including bias and discrimination. This means that the use of neurotechnology devices in Africa holds potential ethical and legal risks to both individuals and society.

As this technology expands, neuroethics and ethics of emerging technology scholars are bringing attention to the critical concerns it raises [4-6]. These concerns are generally not new, but uniquely amplified by the novelty of technology. They include issues around privacy, rights, human identity, autonomy, and safety. Many of these are already part of the ethics of emerging technology discourse, particularly AI ethics. The unique risks this technology raises have led to calls for adequate regulatory oversight. Global discussions in this regard have gained momentum in the last decade with a focus on ensuring responsible and equitable design and deployment of this disruptive technology. Intergovernmental bodies, such as the Organization for Economic Cooperation and Development (OECD), UNESCO (United Nations Educational, Scientific and Cultural Organization), and the Council of Europe, are playing major roles in this regard. Chile has become the first country to implement legal measures that address the risks of neurotechnologies [7]. The Chilean constitution was recently amended to legally protect citizen's mental privacy and free will.

However, as more and more countries discuss the ethics and governance of neurotechnology, there is an obvious lack of regulatory oversight and a dearth of literature on the consideration of contextual ethical principles in the design and application of neurotechnology in Africa. This scenario parallels the historical developments within the field of AI and Africa. In order to circumvent the replication of past errors, this study aims to delineate and address these pitfalls through an in-depth examination and analysis of lessons to be learned. This paper highlights prospective insights that the domain of neurotechnology ethics and governance in Africa may derive from the extant body of literature on responsible AI. Stakeholders, such as neurotechnology developers, policy makers, and academic researchers, stand to gain valuable perspectives from these insights. The resultant impact is anticipated to contribute significantly to the responsible design and implementation of neurotechnology devices in Africa. This encompasses the establishment of robust policies and regulations, as well as the provision of guidance for academic discourse within this domain. This paper starts by providing a conceptual clarification of neurotechnology. Then it discusses why Africa should care about neurotechnology and what responsible neurotechnology will mean for Africa. Lessons are then drawn from the available literature. It is important to note that African societies are not considered as monolithic. However, Africa is taken as a continent with common sociocultural values and challenges relevant to the ethics and governance of neurotechnology.

What is Neurotechnology?

The human brain remains the most complex organ in the human body largely due to its intricate structure and its central role in coordinating all functions and activities of the body. There are many factors that contribute to this exceptional complexity, including its adaptability and plasticity, cognitive abilities, neural network, sensory processing capabilities, motor control, homeostasis, consciousness, genetic complexity, metabolic demand, multilayered structure, and infinite variability. According to Jorgenson et al [8], the goal of comprehensively understanding all these factors "remains elusive, although not from a lack of collective drive or intellectual curiosity on the part of researchers. Rather, progress frequently has been limited by the technologies available during any given era." Neurotechnology has emerged to provide a greater understanding of the brain and offer solutions to previously understudied brain disorders.

UNESCO defines neurotechnology as a "field of devices and procedures used to access, monitor, investigate, assess, manipulate, or emulate the structure and function of the neural systems of animals or human beings" [9]. It involves the application of engineering principles to the "understanding, engagement, and repair of the human nervous system" [10]. Neurotechnology refers to a set of technologies, rather than a specific technology, that enables direct connection or interface between technical components with the nervous system [4,11]. This interaction with the brain and nervous system raises a variety of ethical and legal risks, necessitating the discussion of the ethics of neurotechnology.

The importance of ethics in neurotechnology is demonstrated in UNESCO's call for solid governance of neurotechnology design and deployment at the last international conference on the ethics of neurotechnology on the theme "Towards an Ethical Framework in the Protection and Promotion of Human Rights and Fundamental Freedoms" [12]. From noninvasive technologies used to study the brain to wearable or implantable devices, neurotechnology is opening new possibilities to study the nervous system and help diagnose, treat, and prevent brain-related diseases [1,13]. These technologies are currently being developed for diverse uses in clinical and research settings, as well as for everyday life, workplace well-being, and education. In research, the development of neurosensing technologies, such as magnetic resonance imaging (MRI), functional MRI, electroencephalography, magnetoencephalography, positron emission tomography, functional near-infrared spectroscopy, single-photon emission computed tomography, biomarker analysis tools, and invasive intracranial electrodes, has been transformative for studying the brain. These technologies are fundamental for advancing the understanding of the brain because they provide valuable insights into brain function, neurophysiology, and neurological disorders.

Beyond neurosensing, neurotechnology is also being developed for other purposes, including neurostimulation, neuroprostheses, and neurorehabilitation. Neurostimulation technological devices have shown potential in trials to provide therapeutic relief for

a number of brain-related disorders, such as epilepsy [14], chronic pain [15], Parkinson disease (Schuepbach et al [16]), obsessive-compulsive disorder [17], depression [18], addiction disorders [19], spinal cord injuries [20], and Tourette syndrome [21]. Neurotechnology encompasses invasive and noninvasive devices that serve as motor [22] or sensory [23] neuroprostheses. These devices work by connecting to or bypassing any damaged neural pathways to restore function or enhance communication in people with stroke [24], spinal cord injuries [25], amyotrophic lateral sclerosis [26], cerebral palsy [27], and traumatic brain injuries [28]. When these technologies are designed to help individuals regain lost functional abilities, improve their quality of life, and promote independence, it is called neurorehabilitation [29]. These include noninvasive brain-machine interfaces for patients with stroke [30] to noninvasive interfaces, such as brain-actuated robotic devices designed to restore the independence of people experiencing severe motor disabilities [31].

Indeed, there is an emerging and thriving neurotechnology industry; an industry that reached a market value of US $11.3 billion in 2021 and is projected to exceed US $24.2 billion in 2027, with an estimated annual growth rate of 14.4% [32]. According to a recent UNESCO report, "the United States emerges as the main place where neurotechnology-related innovations are generated (47% of worldwide IP5 patent applications in neurotechnology), followed by Korea (11%), China (10%), Japan (7%), Germany (7%), and France (5%)" [1]. It is further revealed that out of 1400 identified neurotechnology companies, 50% are based in the United States, 35% in Europe and the United Kingdom, and the rest in Asia [1]. These figures are not surprising, given the level of public funding that brain research and innovation are receiving in the Global North. While investments in neurosensing, neurostimulation, neuroprostheses, and neurorehabilitation are different in size, volume, and level of maturity (neurosensing being the most mature and with the highest investments), there are exponential increases in all aspects of neurotechnology.

Why Should Africa Care About Neurotechnology?

Globally, the burden of neurological disorders has increased significantly over the past 2 decades, with a significant increase in mortality (36.7%) and disability (7.4%) rates [33]. There is also evidence from literature to show that there is a large geographical variation in the burden of these disorders [33-37]. There is consistent evidence that there is an increasing prevalence of neurological diseases in Africa, putting huge burdens on public health systems [38-40]. Some of these brain-related diseases include stroke, dementia, Parkinson disease, epilepsy, migraine, medication overuse headache, motor neuron disease, cerebral palsy, brain development disorders, peripheral neuropathy, trauma, alcohol-related brain damage, nervous system complications of HIV/AIDS, brain and nervous system cancers, and multiple sclerosis. It also includes psychiatric disorders and mental health diseases, such as depression, anxiety, schizophrenia, psychosis, bipolar, stress, and other behavioral disorders [41,42]. Many of these are preventable (eg, some developmental disorders and strokes) and others are possibly treatable with novel technologies and therapies.

Silberberg and Katabira [43] believe that the increasing prevalence and burden are the results of factors such as "adverse perinatal conditions, malaria, HIV/AIDS and other causes of encephalitis and meningitis, demographic transitions, increased vehicular traffic, and persistent regional conflicts." In addition to these, there are other factors that increase the impact of neurological disorders in Africa, such as sociocultural and religious beliefs, stigma and discrimination, lack of quality therapies or treatment, and the absence of organized public sector response [40]. Neurological disorders are often neglected or comprehensively ignored in most African societies [44]. Patients in Africa face challenges related to a lack of health care infrastructure and access to specialized services. Many strongly believe that there is no available treatment or therapy for neurological disorders.

Neurotechnology provides hope to African societies struggling with the burden of neurological disorders. It can help bridge the gap in access to neurological care in many underserved communities. They can help with early diagnosis through advanced neuroimaging and diagnostic tools (eg, portable and low-cost electroencephalography machines). Neurorehabilitation tools, such as virtual reality–based therapies [45,46], functional electrical stimulation [47], and telerehabilitation platforms [48], can provide patients access to rehabilitation services in areas with a lack of resources for therapy. A number of neurostimulation devices may possibly provide effective treatment options for patients with epilepsy, while remote computer-based therapies offer possible relief for a number of brain diseases. There are potentially significant opportunities for neurotechnology to have a positive impact on neurological diagnosis, treatment, and rehabilitation in Africa. However, challenges related to cost and infrastructure remain and will need to be overcome.

In addition to clinical support, neurotechnology can also strengthen research in Africa to better understand the epidemiology of neurological disorders, and factors contributing to their prevalence in Africa, as well as improve the global knowledge of the human brain and nervous system. The introduction of neuroimaging data, generated and processed in Africa, can contribute immensely to the global understanding of the brain and its diseases given the genetic diversity in the continent. It implies that brain diseases plaguing the African population will be better understood, raising the likelihood of developing suitable therapies for them. Neurotechnology can also be applied in marketing and consumer research in Africa, especially in the emerging field of neuromarketing. From product testing, pricing, and value perception to emotion analysis and branding, neurotechnology can help companies understand and influence consumer behavior, preferences, and decision-making. Although far-fetched, this can help African businesses to become more competitive in the global market.

Despite the abovementioned potential benefits of neurotechnology, there are also many good reasons for Africa to prioritize other goals and issues, such as cleaning and

sanitation, food security, housing and shelter, education, and access to basic health care. This is a valid argument, and governments need to focus more on these basic needs. However, it is important to note that as a technology, neurotechnology is pervasive, becoming increasingly widespread and influential across various aspects of society. While most of these technologies are being developed outside of Africa, they will be used in Africa. In today's interconnected world, neurotechnologies can spread rapidly across borders through various channels, such as trade, investment, collaboration, and intellectual property agreements. Therefore, the pervasive and ubiquitous nature of this technology makes it hard to neglect.

Furthermore, as UNESCO [12] has observed, the application of neurotechnology triggers a number of critical ethical and legal considerations, including, but not limited to, autonomy, privacy, mental integrity, human dignity, personal identity, and freedom of thought. Given the African sociocultural context and possibilities of using this technology for enhancement, it also raises fundamental questions related to personhood with profound implications for individuals and societies at large. There are also issues around benefit sharing, digital divide, and accessibility and safety concerns. These concerns are amplified by the fact that current neurotechnological systems are being developed with limited data from Africa without consideration of African sociocultural values and principles. For instance, a brain-computer interface that decodes continuous language from noninvasive recordings would have many useful scientific and practical applications [49], but it raises fundamental questions about the privacy of brain data. In a study that in part relies on an AI transformer model, Tang et al [49] claim to have used functional MRI to produce texts of participants' imagined thoughts. The implications this has on privacy are novel and immensely significant in the face of an evident lack of governance mechanisms to ensure that these technologies are designed in an ethically responsible, socially acceptable, and legally compliant way. But what should responsible neurotechnology for Africa look like?

Responsible Neurotechnology in Africa

Like other emerging technologies, neurotechnology raises crucial ethical and legal challenges. However, there remains a dearth of policy frameworks and regulations to ensure the development of responsible and trustworthy neurotechnology. During the UNESCO conference on ethics of neurotechnology in Paris on July 13, 2023, participants agreed on the need for a comprehensive governance framework to harness the potential of neurotechnology and address the evident risks it presents to societies. Speaking at the conference, the Assistant Director-General for Social and Human Sciences of UNESCO declared that "…we must act now to ensure it is not misused and does not threaten our societies and democracies" [12]. In the absence of national, regional, and international principles, policies, and governance mechanisms for neurotechnology, the OECD adopted a set of recommendations on responsible innovation in neurotechnology in 2019 [50]. This is the first attempt to set an international standard that aims to guide government agencies as well as innovators to address the ethical, legal, and social challenges that neurotechnology raises. Principles encompassed in the OECD recommendation are promoting responsible innovation, prioritizing safety assessment, promoting inclusivity, fostering scientific collaboration, enabling societal deliberation, enabling capacity of oversight and advisory bodies, safeguarding personal brain data and other information, promoting cultures of stewardship and trust across the public and private sector, and anticipating and monitoring potential unintended use or misuse. While this instrument does not constitute an international treaty, it covers critical challenges and opportunities for better innovation practices through responsibility-by-design approaches. Such a governance approach is needed to protect and promote human rights and fundamental freedoms. It is an approach that requires the integration of relevant values and principles that reflects the contexts within which the technology will be applied.

So far, the discussion on ethics and governance of neurotechnology has neglected narratives, values, principles, and contexts in Africa. African datasets that can inform the design of neurotechnological systems are currently missing from available open-access platforms. Potentially, therefore, neurotechnology devices are being designed without relevant data from Africa, and the field of neuroscience and neurotechnology remains largely dominated by countries in the Global North. The question then is can responsible neurotechnology be achieved in Africa without African values, principles, data, and experts? Neurotechnology cannot be designed and developed in and for Africa without Africans, their data, and without considerations of African sociocultural contexts, needs, expectations, values, and principles. The current debate on ethics and governance of neurotechnology has taken a similar turn that AI ethics took. Therefore, as UNESCO moves to develop a global normative instrument and ethical framework similar to UNESCO's Recommendation on the Ethics of AI, it is important for policy makers, innovators, and civil society groups to consider these lessons from AI ethics.

Lessons From AI Ethics and Governance

Neurotechnology and AI share some similarities and differences. It is common knowledge that artificial neural networks draw inspiration from the brain structure and function because they are designed with interconnected nodes that loosely mimic how brain neurons interact [51]. Both AI and neurotechnology also involve some forms of learning and adaptation. Similarly, they both have uses in health care. However, there are differences in implementation, complexity, and function. For instance, AI uses chips and programmed algorithms, and is based on mathematical models, while neurotechnology often interacts directly with biological systems (brains and nervous systems).

Brains use biological neurons with complex chemical interactions, while AI uses silicon chips and programmed algorithms. The implication of these differences and similarities is that both AI and neurotechnology share common aims and challenges, but they also demand distinct approaches, methodologies, and considerations. The convergence of the 2 can potentially lead to breakthroughs in understanding the brain as well as both biological and AI, ultimately providing benefits for society. However, attention must be paid to the risks they

raise for which the discourse on ethical considerations of AI is more advanced than in neurotechnology.

In general, neurotechnology can learn valuable lessons from the evolving field of AI ethics and governance to ensure responsible design, development, and deployment. AI ethics debates highlight the need for transparency and explainability in disruptive technological systems to build trust and accountability. Fairness, equity, responsibility, justice, and autonomy are central to AI ethics. These are principles neurotechnology innovators and policy makers need to adopt to ensure that societal needs and contexts are prioritized.

In addition to these, there are also unique lessons for relevant stakeholders designing, developing, and using neurotechnology in and for Africa. These include innovators, neurotechnology industry players, users, and policy makers.

Epistemic Injustice

Neurotechnology, like AI, is a value-laden technology, but the critical question is, and should be, whose values and social contexts shape the design and development of the technology [52]? For a number of decades, AI design, development, deployment, ethics, and governance were based on Euro-American epistemic foundations. Values and principles often discussed in the context of value-sensitive design largely reflected worldviews from the Global North. Narratives, values, and principles from the Global North were mostly forgotten or ignored [53,54]. Ruttkamp-Bloem [55] argues that Africa's exclusion in global AI debates constitutes epistemic injustice that cuts across both hermeneutic and testimonial injustice. This includes the exclusion of African academics and AI practitioners and the work they do in Africa. This lack of diversity, especially in the design and development stage, leads to the exclusion of important knowledge and perspectives from underrepresented communities. Epistemic injustice in AI manifests in different forms including increased bias in AI algorithms, exclusion and marginalization, reinforcement of stereotypes, and other unintended harms. In the context of neurotechnology, this can lead to unfair or inaccurate diagnoses or predictions. Responsible neurotechnology, particularly in Africa, ought to be based on the foundation of epistemic justice—a recognition of Africa's unique contexts, sociocultural and ethical values, principles, and needs. While there might be a need to enhance capacities for neurotechnology design and implementation in Africa, the inclusion of African experts, data, values, contexts, and principles in the design and implementation of neurotechnology is critical to the idea of responsible innovation in neurotechnology.

Principles Alone Cannot Guarantee Responsible Neurotechnology

As the awareness of the risks of AI has risen, private and public institutions have responded with a "deluge of AI codes of ethics, frameworks, and guidelines" outlining high-level principles and values to guide ethical design, development, and implementation of AI [56,57]. Mittelstadt [56] argues that the increasing ecosystem of AI ethics has mostly produced, "vague, high-level, principles, and value statements which promise to be action-guiding, but in practice provide few specific recommendations and fail to address fundamental normative and political tensions embedded in key concepts." The argument here is that AI policy statements and ethical principles have remained ineffective [58] and are largely ignored in many technology-based companies [59]. As Baker and Hanna [60] observed, big technology corporations' "commitments to ethics are hollowed out by vagueness and legal hand-wringing—in practice, they're often merely commitments to maintaining public image and mitigating future public relations disasters." While OECD's principles of responsible innovation in neurotechnology are laudable, these principles are not enough to ensure that innovators and users practically embed relevant values and principles into the design and implementation of neurotechnology. Responsible neurotechnology needs implementable governance mechanisms, that are ethical, legal, and technical. Building on established approaches of translating principles into practice in biomedical sciences, ethics, and governance of neurotechnology should be more robust and rigorous than what we have observed in AI ethics.

Possibilities of Ethics Dumping

Ethics and governance of these technologies help to anticipate potential risks, promote safe innovation and deployment, and prevent use that violates core values or exposes people to unacceptable risks. As AI governance has gained momentum in the Global North, Ruttkamp-Bloem [55] believes that Africa has become the ethical dumping ground of the main players on the AI technology scene because of weak regulations. Ethics dumping here refers to the practice of carrying out unethical or legally nonpermissible research activities in countries or regions with weak or nonexistent regulations or governance frameworks. In AI, there is emerging evidence of ethics dumping in the form of "health data colonialism," in which AI researchers and developers from big technology companies collect data from developing countries to build algorithms in these countries to avoid stricter regulations in their countries [61]. Another example is the outsourcing of data labeling by OpenAI to Africa in what has been called labor exploitation and "unethical outsourcing" [62].

These are possible scenarios that can happen with neurotechnology. As countries in the Global North continue to discuss possibilities of neurorights and governance of neurotechnology, there is a likelihood that neurotechnology companies will exploit the nonexistent regulatory framework in Africa, from unethical human testing to labor exploitation. Africa needs to be aware of this and become proactive in considering governance mechanisms to guide the design, development, and deployment of neurotechnology.

Diversity of Datasets Is of Critical Importance

The diversity of datasets in the design of emerging technologies is of paramount importance. Diverse datasets offer a more accurate representation of the real world and help to ensure that the technology is fair, robust, inclusive, effective, and sustainable. Fairness, equity, and generalizability in AI mostly depend on how representative the data used to train the AI system are. Nonrepresentative datasets infuse bias into the system. It is also common knowledge that without datasets from AI, AI cannot work for Africa. The quality, quantity, and

diversity of data from Africa play a crucial role in the development of accurate, reliable, and generalizable AI systems in Africa. This is the same with neurotechnology. Racially exclusionary practices have been attributed to nanotechnological devices used for neuroimaging, both in the acquisition and analyses [63-65]. Many electroencephalography devices are simply not designed with black hair in mind, which creates implicit racial bias. This means that these devices were designed with insufficient data from black people. It is important for neurotechnology innovators to focus on using sufficient and relevant data from Africa in the design. Africa needs to focus more on generating and having ownership of Findability, Accessibility, Interoperability, and Reusability (FAIR) datasets that can contribute to the design and development of neurotechnology in and for our societies [66].

Inadequate Regulatory Frameworks

One lesson from the recent AI boom in Africa is that many countries still lack a strong regulatory framework to address the challenges that emerging technologies like AI raise. While existing regulatory frameworks, such as data protection regulations, provide potential channels for integrating regulatory aspects of AI, the rapid advancements of this technology have outpaced the scope of these laws. The European Union's AI Act has shown that to accommodate the dynamics of such a disruptive technology, a dedicated regulatory mechanism is required. Neurotechnology has been described as a disruptive innovation that will disrupt existing practices as well as traditional boundaries between medical therapies and consumer markets [67]. It has the potential to cause profound social and legal disruption. Owing to their increased capabilities aided by improved computational ability, machine learning, AI, and the availability of large-scale open-access databases, these technologies have the potential to become critical to future legal systems. There are possibilities of using them to predict the likelihood to recidivate, assess volition and intent, detect lies, as well as the potential to reduce recidivism [68]. There are concerns related to mental privacy and surveillance (especially workplace mental surveillance), issues related to equity, and other aspects of personal liberties, which may not fully be captured by existing regulations. Unlike in the case of AI, Africa does not need to play catch up. Relevant stakeholders, including policy makers and researchers, should be proactive in scrutinizing advances in neurotechnology. The time to act is now. There is a great need to develop an effective regulatory or governance framework that can promote responsible neurotechnology in a way that safety, ethical, and legal concerns are sufficiently addressed.

Regulations are important here because this is a technology that challenges existing laws and belief systems. There have been claims in the literature that the risks neurotechnology poses to fundamental freedoms of thought and expression demand new regulations to protect cognitive liberties [69] or neurorights [70]. The risks are significantly exacerbated by the increasing application of neurotechnology in the military as well as the consumer market for digital phenotyping, emotional information, neurogaming, and neuromarketing. These use cases highlight the possibilities of exerting control over brain activities and individual thoughts, which raise the risks of dual use of concern, digital mental surveillance, misuse of neurodata, and other privacy issues. As AI has shown [71], this technology surpasses the ability of existing laws, including data protection laws, to govern its design and development. This paper certainly does not make a case for neuroright laws but seeks to highlight the need to establish regulatory frameworks or amend existing ones that can make neurotechnologies align with African societal values and contexts.

Available Data Protection Regulations Are Inadequate

The global landscape of data protection regulation is significantly expanding, driven by increasing awareness of privacy issues and the need to regulate the growing digital ecosystem. Most importantly, the introduction of the European General Data Protection Regulation in 2018 is greatly influencing the global approach to data protection with its stringent requirements and extraterritorial scope. So far, over 30 African countries have established data protection laws and or regulations. It is important, however, to note that while data protection regulations play a crucial role in safeguarding the privacy of the individuals, the unique challenges posed by neurotechnology require additional measures and considerations [72,73]. Yuste [74] have raised awareness of the ability of implantable and nonimplantable neural devices to record and alter brain data in ways that jeopardize personal neuroprivacy. There is evidence in the literature to suggest that these devices can successfully decode mental imagery, emotions, story interpretation, and speech [49,75-77]. There are apparent voids in existing data protection regulations to address some of the complex issues involved here. They are not fully aligned to address specific risks and implications associated with the collection and application of brain data by neurotechnology.

To address this gap, some have proposed the establishment of novel human rights, neurorights [70,78], due to concerns around mental privacy, mental integrity, and cognitive liberty. Others have proposed a data-centered approach focused on revising data protection regulations to incorporate issues raised by neurotechnology [79]. As the landscape of neurotechnology continues to progress in Africa, it is important for African policy makers to understand that the available regulations and laws on data are not adequately equipped to address the complex ethical and legal issues neurotechnology raises. While the option of novel human rights is globally being discussed, the data protection–centered approach may be the most pragmatic approach to address the immediate, data-related risks involved in neurotechnology, given the claim for the exceptionalism of neurodata [80].

The Need for Stakeholder Engagement

At present, the debate over AI governance and regulation in Africa is being shaped by scientists, lawmakers, and scholars in the humanities and the social sciences. However, such debate tends to often lack representation from key stakeholders, which are citizens and community members, who are using these technologies and who will be subject to these new rights. There is a growing consensus among scholars, national governments, and technology corporations about the need to recognize and involve the public as active participants in the design of AI governance [81]. This is often discussed as the democratization

of AI or algorithms [82]. AI can have profound impacts on culture, society, and citizens' rights. Public engagement ensures that these impacts are proactively considered and that the established governance mechanisms reflect the values and priorities of those who will use them. Similarly, ethics and governance of neurotechnology in Africa will benefit greatly from public engagement, not only to raise awareness and understanding of the technology but also to inform the development of governance frameworks that are responsive to the needs and concerns of the public. Public engagement broadens the range of voices that can provide insights to better anticipate potential risks of the technology. It is important that such public engagement exercises are established to ensure public trust which is critical to technology acceptance.

The Possibility of Corporate Capture

In the absence of functional governance frameworks for responsible AI, technology companies have taken the lead by funding most of the global AI ethics research. This provides an opportunity to influence the research agenda [83]. This is what Gerdes [84] called corporate colonization of the AI ethics research agenda. Large parts of the global AI ethics research are funded by big technology companies fundamentally more interested in their profits rather than public interest [85]. Gerdes [84] also identifies conflicts of interest in AI public policy–making initiatives. Leveraging weak or nonexistent funding mechanisms, regulations, and institutions in Africa, there is a possibility for big neurotechnology companies to control research on ethics and governance of neurotechnology in Africa. Neurotechnology industry players can capture the narrative or discussion on the ethics of neurotechnology to their own benefit. This will have grave consequences in real life. The ethics and governance of neurotechnology, particularly in Africa, need multistakeholder engagement and less performative efforts from policy makers and innovators. It also needs independent (free from the big technology influence) research efforts that will not only inform governance but that can build a sustainable human and technical infrastructure in Africa.

Dangers of Overly Anthropomorphizing Technology

Human-technology interactions have shown that there is always a tendency to anthropomorphize technology [86]. Indeed, anthropomorphism has become part of the AI literature [87-89]. This is the attribution or projection of humanlike characteristics to inanimate objects, animals, and in this case technology [90]. This is a cognitive bias [91] informed by sociocultural awareness and beliefs. Anthropomorphizing AI can lead to unrealistic expectations and overtrust of the technology. It can blur the lines between humans and machines and consequent attribution of moral agency to machines. As a technology that can interface between the brain and computers, certain neurotechnological devices are developed to create more humanlike interactions. This raises the possibility of overly anthropomorphizing the technology, particularly in Africa, where anthropomorphism is already part of the cultural fabric through religion. This can lead to misconceptions of their capabilities and limitations, raising ethical and practical concerns. To mitigate the negative impacts of the anthropomorphism of neurotechnology, innovators and policy makers need to choose between creating user-friendly neuro-interfaces and maintaining transparency about the nature, capabilities, and limitations of the technology. This includes the education of relevant stakeholders on the roles, nature, and constraints of neurotechnology.

Conclusion

This paper makes an argument that neurotechnology is no longer a future technology; it is here and is now available not only for clinical research and practice but also to consumers. It is revolutionizing our understanding of the brain and its diseases; providing much needed therapies for a wide range of patients are increasingly used in direct-to-consumer products. Some of these technological devices are being designed in and for Africa [92]. However, the rapid advancement of this technology raises serious risks concerning safety, privacy, human rights, digital divide, bias, and discrimination. With evident weak or nonexistent ethical and regulatory institutions capable of ensuring responsible development and use in Africa, individuals and the society at large face serious risks. Without putting Africans and their needs, interests, values, principles, contexts, data, and expectations into consideration in its design and governance, neurotechnology risks discriminating against Africans as well as jeopardizing the privacy and safety of citizens. This is similar to what is happening in the field of AI. Stakeholders, including policy makers, innovators, and users, can learn the above lessons from AI ethics and governance to ensure that proactive actions are instituted to mitigate against the risks neurotechnology presents to Africans. These lessons need to be taken into consideration as public debates and governance mechanisms for neurotechnology are shaped in Africa. Proactivity and collaboration are the key to being responsive to the demands of mitigating the risks this technology poses. Researchers and scientists working in Africa also need to focus on providing evidence-based insights that can inform policy and practice. This includes consistently providing users and citizens in general with the awareness of the benefits and risks of neurotechnology, which is becoming the new and disruptive technology frontier.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
FAIR: Findability, Accessibility, Interoperability, and Reusability
MRI: magnetic resonance imaging
OECD: Organization for Economic Cooperation and Development
UNESCO: United Nations Educational, Scientific and Cultural Organization

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Viewpoint

Twenty-Five Years of AI in Neurology: The Journey of Predictive Medicine and Biological Breakthroughs

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Abstract

Neurological disorders are the leading cause of physical and cognitive disability across the globe, currently affecting up to 15% of the world population, with the burden of chronic neurodegenerative diseases having doubled over the last 2 decades. Two decades ago, neurologists relying solely on clinical signs and basic imaging faced challenges in diagnosis and treatment. Today, the integration of artificial intelligence (AI) and bioinformatic methods is changing this landscape. This paper explores this transformative journey, emphasizing the critical role of AI in neurology, aiming to integrate a multitude of methods and thereby enhance the field of neurology. Over the past 25 years, integrating biomedical data science into medicine, particularly neurology, has fundamentally transformed how we understand, diagnose, and treat neurological diseases. Advances in genomics sequencing, the introduction of new imaging methods, the discovery of novel molecular biomarkers for nervous system function, a comprehensive understanding of immunology and neuroimmunology shaping disease subtypes, and the advent of advanced electrophysiological recording methods, alongside the digitalization of medical records and the rise of AI, all led to an unparalleled surge in data within neurology. In addition, telemedicine and web-based interactive health platforms, accelerated by the COVID-19 pandemic, have become integral to neurology practice. The real-world impact of these advancements is evident, with AI-driven analysis of imaging and genetic data leading to earlier and more accurate diagnoses of conditions such as multiple sclerosis, Parkinson disease, amyotrophic lateral sclerosis, Alzheimer disease, and more. Neuroinformatics is the key component connecting all these advances. By harnessing the power of IT and computational methods to efficiently organize, analyze, and interpret vast datasets, we can extract meaningful insights from complex neurological data, contributing to a deeper understanding of the intricate workings of the brain. In this paper, we describe the large-scale datasets that have emerged in neurology over the last 25 years and showcase the major advancements made by integrating these datasets with advanced neuroinformatic approaches for the diagnosis and treatment of neurological disorders. We further discuss challenges in integrating AI into neurology, including ethical considerations in data use, the need for further personalization of treatment, and embracing new emerging technologies like quantum computing. These developments are shaping a future where neurological care is more precise, accessible, and tailored to individual patient needs. We believe further advancements in AI will bridge traditional medical disciplines and cutting-edge technology, navigating the complexities of neurological data and steering medicine toward a future of more precise, accessible, and patient-centric health care.

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KEYWORDS

neurology; artificial intelligence; telemedicine; clinical advancements; mobile phone

Introduction

Neurological disorders are a leading cause of disability and mortality worldwide, affecting millions of individuals and placing a significant burden on health care systems. In 2019, these disorders were responsible for nearly 10 million deaths and 349 million disability-adjusted life-years globally, with stroke and neonatal encephalopathy being the primary contributors [1,2]. Over the past 3 decades, the prevalence of neurological disorders has increased substantially, particularly in low- and middle-income countries, and this trend is expected to continue as populations age [1]. However, we have also witnessed remarkable advancements in technology and data science that are transforming the field of neurology. These developments offer new hope for improving the diagnosis, treatment, and management of neurological disorders. This paper explores the evolving landscape of neurology, focusing on how the integration of cutting-edge technologies and vast datasets is revolutionizing our understanding of neurological disorders and paving the way for more personalized, effective, and accessible care.

In the past 25 years, numerous technological advancements have significantly impacted the field of neurological medicine. These advancements include the integration of cutting-edge imaging technologies that offer deeper insights into brain anatomy, physiology, and function; the use of advanced electrophysiological techniques to create detailed brain region and connectivity maps; breakthroughs in neurogenetics and molecular biology that aid in identifying and characterizing neurological conditions; and the expansion of telemedicine, which allows physicians to deliver more efficient and accessible care.

Specifically, one of the most notable advancements has been the widespread adoption of electronic health records (EHRs). EHRs have not only transformed clinical practice but also opened up vast opportunities for research by creating large datasets that can be analyzed using advanced data science techniques. The integration of EHRs with other data sources, such as imaging and genetic data, has enabled researchers to identify novel disease subtypes, predict patient outcomes, and develop personalized treatment strategies. Another area where technology has made significant strides is in the development of novel diagnostic tools and biomarkers. For example, advances in neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans, have facilitated more accurate diagnosis of neurological diseases. Similarly, the discovery of new genomic and molecular biomarkers has paved the way for more targeted therapies and precision medicine approaches. Furthermore, the increasing availability of large-scale neurological datasets, coupled with advancements in machine learning and artificial intelligence (AI), has opened new possibilities for predictive and decision support systems. These tools can assist clinicians in making more accurate diagnoses, predicting disease progression, and optimizing treatment plans based on individual patient characteristics.

It is important to acknowledge that while this paper aims to provide a comprehensive overview of the impact of AI on neurology, its scope is necessarily limited. We have focused on key areas that, in our assessment, have most significantly influenced the field of neurology over the past quarter-century. The subsequent 5 chapters of this paper dive deeper into these advancements, exploring how they are reshaping the landscape of neurological care and research (Figures 1 and 2). Rather than attempting an exhaustive analysis of each topic, our goal is to highlight the current state of the art, identify pressing challenges and promising opportunities, and suggest potential future directions within each domain. By doing so, we hope to provide a balanced perspective on the transformative potential of AI in neurology, while also recognizing the vast and rapidly evolving nature of this field. This paper serves as a starting point for further exploration and discussion, acknowledging that the integration of AI in neurology is an ongoing journey with many exciting developments yet to come.

Figure 1. Fields of advances in the last half-century in neurology. AI: artificial intelligence; CT: computed tomography; EHR: electronic health record; GWAS: genome-wide association study; MRI: magnetic resonance imaging; NGS: next-generation sequencing; PET: positron emission tomography; RNA-seq: RNA sequencing.

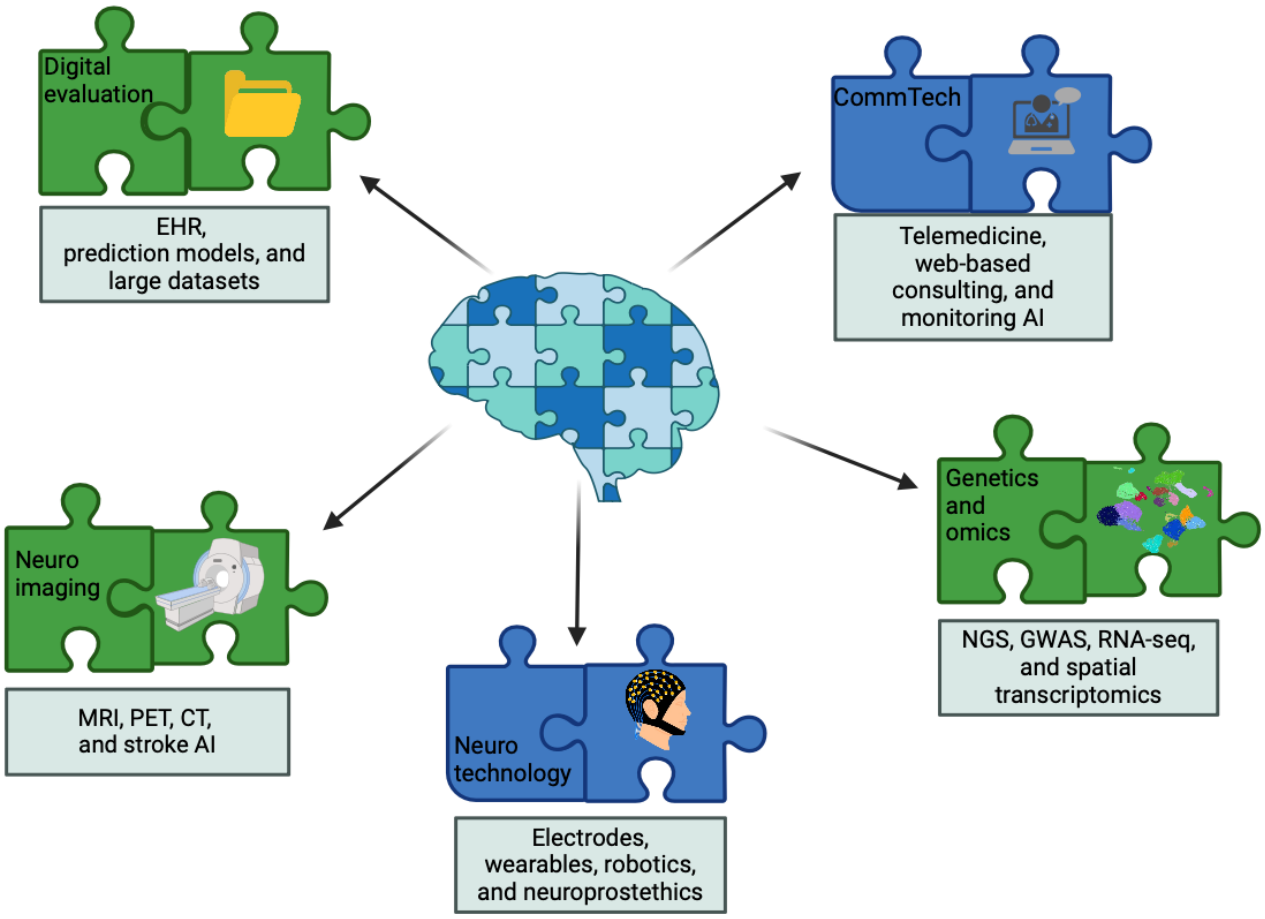
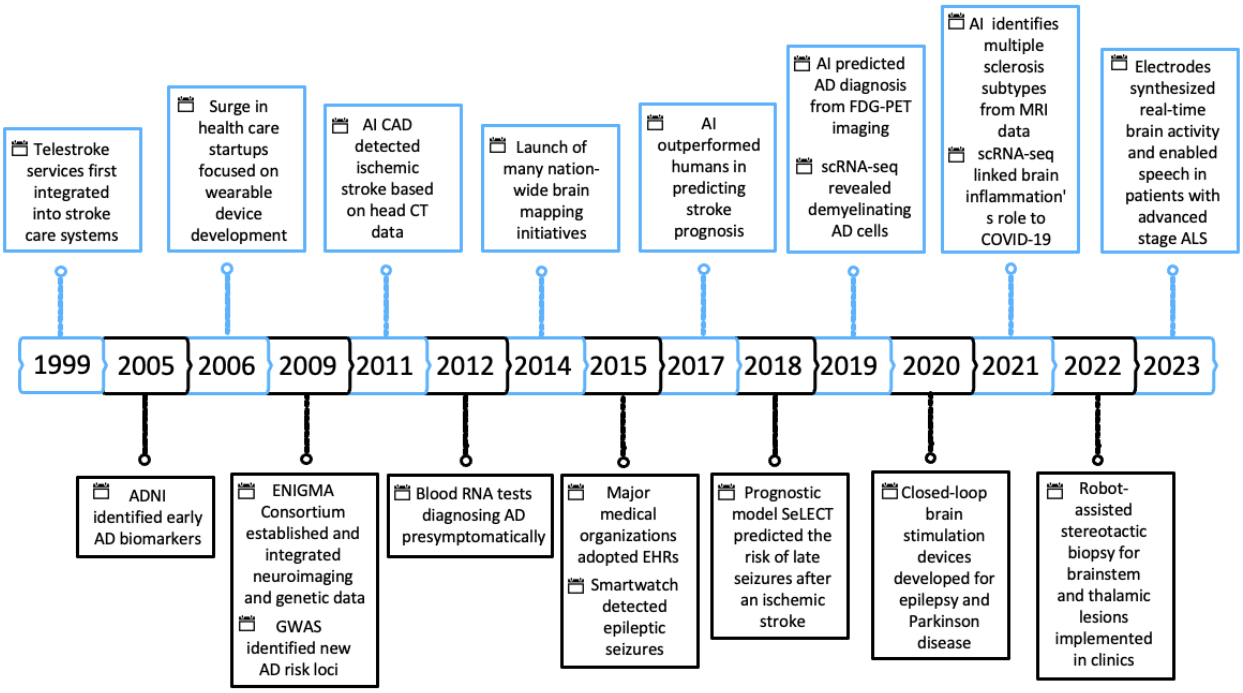


Figure 2. Timeline of key technological advances in the last 25 years. AD: Alzheimer disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; AI: artificial intelligence; ALS: amyotrophic lateral sclerosis; CAD: computer-aided design; CT: computed tomography; EHR: electronic health record; ENIGMA: Enhancing NeuroImaging Genetics through Meta - Analysis; FDG-PET: fluorodeoxyglucose-positron emission tomography; GWAS: genome-wide association study; MRI: magnetic resonance imaging; NIH: National Institutes of Health; scRNA-seq: single-cell RNA sequencing; SeLECT: severity of the stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery.



The Digital Transformation of Neurological Evaluation: From Bedside Physical Examination to Data-Driven Diagnostics

Overview

The transition from traditional physical examination to digital data acquisition and patient triage in outpatient clinics marks a significant paradigm shift in neurological evaluation. It is widely accepted that a meticulous patient history is crucial for achieving an accurate and timely diagnosis, with estimates suggesting that 70% to 90% of medical diagnoses can be determined by history alone [3]. This, combined with a physical examination and a comprehensive understanding of neuroanatomy, constitutes a traditional approach to neurological diagnosis, primarily aimed at pinpointing the disease's anatomical location. The specific features that make neurology unique include a heavy reliance on complex physical examination for diagnosis and follow-up, use of specialty-specific neurophysiologic testing (eg, electromyography or nerve conduction studies, electroencephalogram [EEG], sensory evoked potential studies, and sensory evoked potentials), high use of neuroradiologic imaging such as magnetic resonance imaging (MRI) and computed tomography (CT), use of videotaped examinations by clinicians for movement disorders, use of patient-recorded videos or pictures in the medical record (eg, seizures, pseudoseizures, tics, and dyskinesias), and importance of patient documentation of episodic complaints (eg, migraines and seizures).

While traditional approaches have been the backbone of neurological practice, the rapid growth of digital technologies and the increasing volume of patient data have necessitated a shift in how neurologists approach diagnosis and treatment. The digitization of medical records, in particular, has been a game changer, allowing clinicians to capture, store, and analyze vast amounts of patient information in ways that were previously unimaginable. This transition has not only improved the efficiency and accuracy of neurological care but also opened up new avenues for research and discovery.

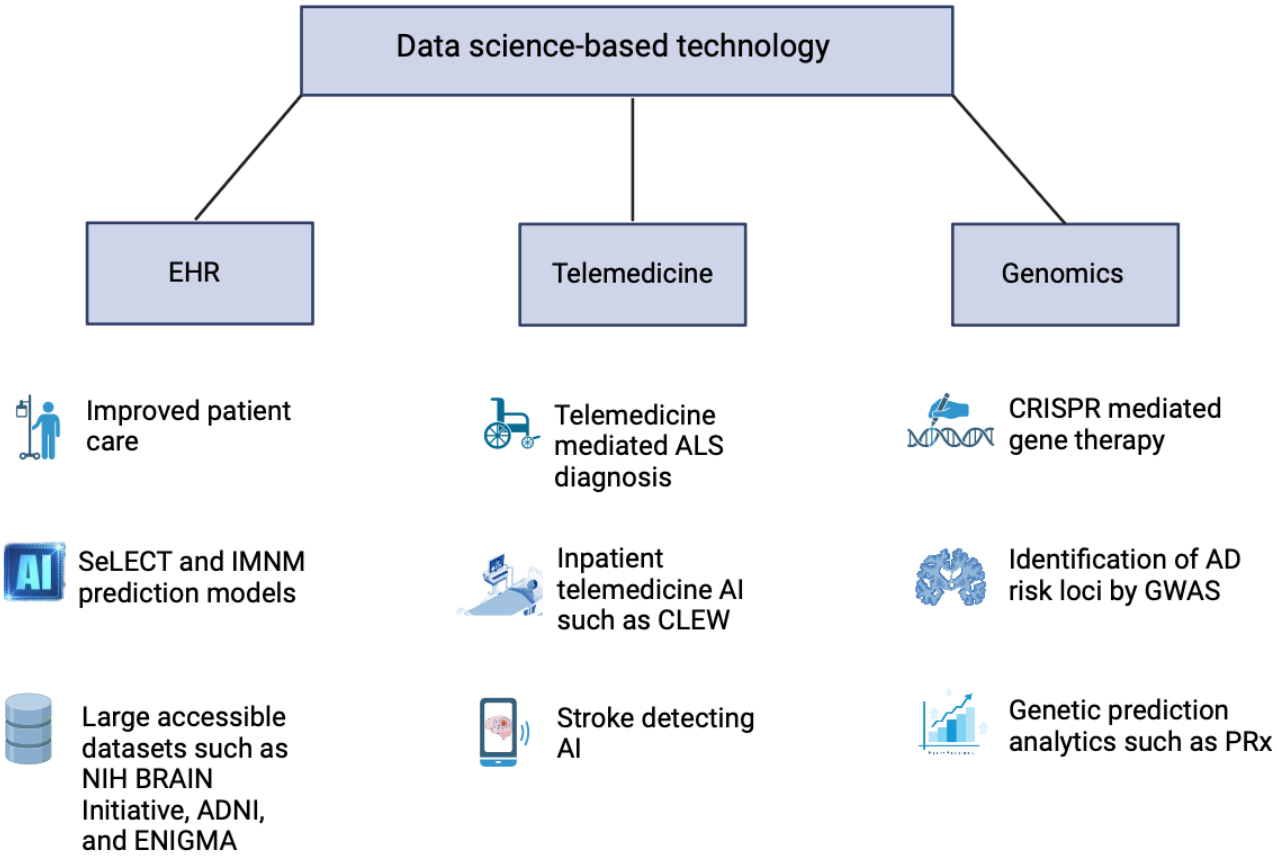
The adoption of EHRs has been a gradual process, driven by advances in computing technology and the recognition of their potential to improve patient care. The journey began in the 1960s with the earliest attempts to digitize patient information, but it was not until the 1990s that electronic medical records began to gain widespread traction. In the 1990s, the rise of more affordable, powerful, and compact computing technologies, alongside the increasing use of local area networks and the internet, catalyzed the development and adoption of electronic health and medical records, also known as EHRs [4]. Initially, EHRs were predominantly deployed in academic medical facilities, containing only partial medical information, with the remainder still documented on paper [5]. These early systems were mainly hosted on large mainframes with limited functionalities, focusing on laboratory and medication [6]. Their adoption faced challenges due to high costs, data-entry errors, and only partial acceptance by physicians [7]. At this stage, EHRs were primarily used for data interchange among physicians [8] and for image scanning and documentation [9], with clinical use increasing as computers became more integrated into health care as "physician workstations" [10].

There has been rapid adoption of EHRs over the last few years, spurred largely by financial incentives allocated by the Health Information Technology for Economic and Clinical Health Act as part of the American Recovery and Reinvestment Act of 2009. In the years that have since passed, the global use and reliance on EHRs in departments such as the emergency department have grown stronger. By 2015, EHRs had gained recognition from major medical organizations and governments as essential for storing patient data to optimize care delivery [11]. This app endowed the hospital with improved web or client-server–based systems with relational databases, facilitating easier data access and the sharing of medical information through health information exchange networks [12]. This period also saw efforts to standardize EHRs internationally, allowing for a common set of data exchange standards and terminology. In outpatient clinics, there is a consensus that the integration of EHR has resulted in a significant reduction in overall waiting times and a decrease in documentation errors [13].

Improved Patient Care and Triage in Neurology

The implementation of EHR system has fundamentally altered both research paradigms and clinical workflows for neurologists (Figure 3). The EHR system, by its very design, has transformed the way neurologists compose clinical notes, often replacing individualized communication styles with template-based entries that aggregate vast amounts of data with minimal effort. Neurologists have written about the challenges of EHR use with many published articles discussing the difficulties in neurology practice. Recent publications report concerns with the efficiency of the use of EHRs in academic practice, challenges of implementation, improper documentation, issues of privacy, and impairing the physician-patient relationship.

Figure 3. Summary of neurology-related data science–based advances in the last half-century. AD: Alzheimer disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; AI: artificial intelligence; ALS: amyotrophic lateral sclerosis; CRISPR: clustered regularly interspaced short palindromic repeats; EHR: electronic health record; ENIGMA: Enhancing NeuroImaging Genetics through Meta - Analysis; GWAS: genome-wide association study; IMNM: immune-mediated necrotizing myopathy; NIH: National Institutes of Health; PRx: pressure reactivity index; SeLECT: severity of the stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery.



The adoption of EHRs has had a significant impact on the field of neurology, along with the broader medical community, influencing everything from clinical practice and patient care to research and administration. EHR systems have standardized the documentation process, making it easier to maintain consistency across patient records. This is particularly beneficial in neurology, where the complexity of neurological conditions requires detailed recording of clinical findings, treatment plans, and patient responses. However, the standardization can sometimes lead to a loss of individual clinician's nuances in documenting their observations and thought processes, potentially impacting the richness of the clinical narrative. Another area is accessibility and coordination of care, which allows for easier access to patient records across different health care settings, which is crucial for neurology patients who often require multidisciplinary care. This accessibility improves coordination among health care providers, leading to more integrated care plans and better patient outcomes. Furthermore,

EHR systems have facilitated the growth of telemedicine, which has become especially important for neurology patients with mobility issues or those living in remote areas. One overwhelming success is the wealth of data captured in EHRs that can be a gold mine for neuroinformatic research and the development of predictive models for neurological diseases. This aspect is particularly relevant in academic and research settings where EHR data can be analyzed to uncover patterns, predict outcomes, and guide the development of new treatment protocols [14].

Prediction Models Using Electronic Records

In this current era of big data, the focus has shifted toward leveraging the vast databases of EHRs through AI and machine learning technologies. This involves developing AI algorithms for predicting patient risk and personalized treatment plans [15]. One example is a study that focuses on addressing the gap in predicting poststroke seizures, a significant concern in neurology given stroke's role as a leading cause of acquired epilepsy in adults [16]. The researchers aimed to develop and validate a prognostic model, named the SeLECT score ("Se" severity of the stroke, "L" large artery atherosclerosis, "E" early seizure, "C" cortical involvement, and "T" territory of the middle cerebral artery), for predicting the risk of late seizures (occurring more than 7 days after) in individuals who have had an ischemic stroke. The SeLECT score was developed through a multivariable prediction model using data from 1200 participants in Switzerland and validated externally in 1169 participants across Austria, Germany, and Italy. It incorporates 5 clinical predictors: severity of stroke, large-artery atherosclerotic etiology, early seizures, cortical involvement, and territory of middle cerebral artery involvement. The model's effectiveness was demonstrated by its ability to stratify the risk of late seizures after stroke with a concordance statistic of 0.77 in validation cohorts, indicating good predictive accuracy. This approach exemplifies the potential of predictive models to transform patient care in neurology by enabling tailored interventions based on individual risk assessments [16].

Another example is a study that introduces a statistical model designed to improve the diagnosis of immune-mediated necrotizing myopathy (IMNM), a condition where delayed diagnosis can lead to significant morbidity. In a subset of IMNM diagnosis is particularly challenging as in patients describe chronic course and lack specific symptoms. The model leverages electrical myotonia versus fibrillations as biomarkers to predict immunotherapy treatment response, based on data from 119 cases of IMNM and 938 other patients with myopathy. All patients underwent electrophysiological evaluations, muscle biopsies, neurological examinations, and creatine kinase measurements [17]. In the broader context of predictive models in neurology, this study exemplifies how statistical models can significantly enhance the diagnosis and treatment of neurological conditions. By identifying specific biomarkers and incorporating them into a predictive framework, such models offer a path toward more personalized and timely interventions. This approach mirrors the potential seen in the SeLECT score for predicting poststroke seizures, further illustrating the critical role of predictive models in advancing neurology practice.

Predictive models may also incorporate other types of data, including imaging, biomarkers, and environmental and lifestyle factors. The scope of predictive models is broad; in cerebral hemodynamics, they focus on assessing cerebral autoregulation to determine the optimal cerebral perfusion pressure for individual patients. For example, the pressure reactivity index [18] uses data from ventricular catheters [19] or intraparenchymal devices [20]. Cerebral metabolism is another area benefiting from predictive analytics, with algorithms analyzing brain interstitial fluid via intracerebral microdialysis to detect metabolic distress, anaerobic metabolism, cell injury, and membrane breakdown. This monitoring facilitates early detection of metabolic changes and guides therapeutic interventions [21]. In addition, predictive analytics plays a critical role in brain oxygenation monitoring, ensuring a balance between oxygen supply and demand. The primary methods in this field include direct brain tissue oxygen tension monitoring [22], jugular venous bulb oximetry [23,24], and near-infrared spectroscopy [25]. Moreover, in recent years, the development of predictive analytics for neurological disorders has seen significant advancements. For instance, researchers have derived a single "Alzheimer Disease Identification Number" from clinical and neuroimaging data, offering a novel approach to tracking disease severity [26]. In multiple sclerosis (MS), a developed predictive model can identify MS subtypes through MRI data and unsupervised machine learning [27]. In Parkinson disease (PD), predictive models have identified antitumor necrosis factor therapy as a potential therapeutic option for mitigating disease risk among patients with inflammatory bowel disease [28]. These advanced analytics methods demonstrate improved accuracy and prognostication over traditional models, offering new insights into patient management and treatment outcomes in neurovascular research.

This shift toward health care institutions taking on the responsibility for developing decision support tools marks a significant point in the regulatory environment and the need for tailored solutions. At the same time, the global health care sector is increasingly tapping into EHR data for AI-based projects, aiming to use the vast amount of medical data to enhance patient outcomes through disease prediction, treatment personalization, and the acceleration of new drug discovery especially in neurology. These efforts require strict protocols for data standardization, processing, and privacy to maximize the benefits of AI research while protecting sensitive patient information. Supported by initiatives such as those from the Korean government [29,30], there is a growing movement toward leveraging AI in health care, pointing toward a future where AI, powered by EHR data, becomes central to advancing medical research and delivering personalized care to patients.

Creation of Large Accessible Datasets

Despite the critical importance of training databases, there is a lack of publicly accessible, reliable datasets. This shortage primarily results from data sharing barriers across institutions, the time and cost of data annotation, and occasionally, the complexity of building data processing pipelines. Training data may be preannotated, a process known as "supervised learning," or it may not be, which is referred to as "unsupervised learning." In the realm of AI in health care, supervised learning models

are predominantly used due to the critical nature of their applications, where human lives hinge on the accuracy of AI outputs. To address this issue, several national and multinational data banks have emerged, covering various neurological conditions [31]. From 2013 to 2014, several governments initiated national initiatives aimed at understanding brain function, such as the National Institutes of Health (NIH) BRAIN Initiative [32], the Human Brain Project [33], and the Brain Mapping by Integrated Neurotechnologies for Disease Studies project in Japan [34]. Many of them soon became global and involved collecting and analyzing voluminous data, including neuroimaging, genetic, biospecimen, and clinical assessments, to unlock and decipher the genesis and prognosis of neurological conditions. As the collection of data became increasingly prominent, the need for procedures, standards, hardware, and software for data-intensive computing increased [35]. These projects leverage big data to explore the brain structure ("connectome") and function with the ultimate goal of developing new treatments for neurological diseases.

For instance, the Alzheimer's Disease Neuroimaging Initiative (ADNI), which was launched in 2005, aims to identify biomarkers for the early detection and monitoring of Alzheimer disease (AD). It supports interventions, prevention, and treatments through early diagnostics and facilitates global data sharing [36,37]. By collecting and analyzing data on cognitive functions, brain structure, metabolism (via PET and MRI scans), genetics, and biochemical changes in a diverse cohort, ADNI has provided significant contributions. Its most substantial contribution to date is the development of methodologies for the early diagnosis of AD using biomarker tests, such as amyloid PET scans and cerebrospinal fluid lumbar punctures. This approach has revealed a significant number of individuals in their mid-70s showing preclinical stages of AD [38], underscoring the critical importance of early prevention and treatment strategies for the disease.

In parallel, the Enhancing NeuroImaging Genetics through Meta‐Analysis Consortium [39], established in 2009, represents another pivotal big data initiative in the field of neuroscience. It aims to integrate neuroimaging and genetic data to investigate brain genotype-phenotype relationships. Notable achievements of the Enhancing NeuroImaging Genetics through Meta‐Analysis consortium include identifying genome-wide variants related to brain imaging phenotypes [40,41] and examining MRI-based abnormalities across various conditions [39,42] such as major depressive disorder [43] and bipolar disorder [44]. These discoveries have substantially improved diagnostics and patient care, showcasing the value of integrating big data in advancing neuroscience research.

Beyond the contributions of major organizations, recent years have witnessed the emergence of numerous big data–driven diagnostic solutions in neuroscience from smaller entities. Key discoveries include the identification of MS subtypes using sophisticated imaging analyses and improvements in MRI data [27] and unsupervised machine learning as well as the differentiation of dementia subtypes through the analysis of multimodal data from ADNI [45]. In addition, significant strides have been made in depression research, highlighted by the successful prediction of treatment response through various methods: connectome gradient dysfunction paired with gene expression [46], resting state connectivity markers of transcranial magnetic stimulation response [47], and a sertraline-response EEG signature [48]. In terms of migraine research, the Italian Migraine Registry is being developed to serve as a comprehensive source of clinical, biological, and epidemiological big data. This registry aims to enhance our understanding of therapeutic response rates and the efficacy of treatments [49]. Another notable diagnostic initiative is the iPrognosis mobile app designed to expedite the diagnosis of PD and improve the quality of life for patients with PD. The app functions by collecting data during the user's interaction with smart devices, including smartphones and smartwatches, showcasing the innovative use of technology in patient care and research [50].

In summary, over the past decade, numerous emerging AI technologies have significantly enhanced patient flow through various means. These advancements range from facilitating direct intrahospital communication to autonomously analyzing radiological images and assisting in the selection of patients for specialized treatments. The development and refinement of these AI systems rely heavily on access to extensive data banks, which serve as foundational resources for training purposes. Such repositories, both large and small, have already yielded substantial improvements in the diagnosis of numerous neurological conditions. The trend toward leveraging big data is expected to intensify, with the emergence of larger databases in the coming years. This expansion will be further supported by an increasing volume of data collected through wearable technology. Consequently, these databases will play a crucial role in enabling the development of new AI-driven approaches for treatment and diagnosis [51].

New Communication Technologies: Telemedicine and Remote Patient Monitoring

Overview

As powerful an approach as AI-mediated medical treatment is, it still does not fully address the growing demand for neurological care, which is exacerbated by a shortage of neurologists. This challenge is expected to intensify with the expanding aging population, highlighting the urgent need for a more substantial neurological care provision. Telemedicine emerges as a promising solution to bridge this gap, offering access to those hindered by geographical or physical barriers such as mobility issues (Figure 3). It facilitates earlier access to specialized care, potentially reducing the strain on patients and caregivers while enhancing patient satisfaction. In addition, telemedicine provides an avenue for neurologists facing social, physical, or health-related challenges to maintain or extend their practice, including those considering part-time work or retirement. It also allows for more efficient use of neurologists' time by eliminating travel between facilities, thereby increasing their availability for patient evaluations and the ability to serve remote clinics. Telemedicine leverages a wide array of technologies, including 2-way videoconferencing, data storage and forwarding, and mobile and wireless devices, to deliver

care more flexibly and efficiently [52]. Despite previous barriers to telemedicine adoption, such as reimbursement issues, recent policy changes by the Centers for Medicare and Medicaid Services, which expanded Medicare-covered telehealth services for 2019, have significantly improved access to neurological care. These changes not only enhance patient care options but also open new revenue streams for neurologists, signaling a shift toward a more accessible and sustainable model of neurological care delivery [53,54].

Virtual Consultations

Telestroke services, first described in 1999 and formally integrated into stroke care systems for over a decade, have significantly influenced the broader field of telemedicine. This period has seen expanded access to care, improvements in quality, and higher rates of reperfusion therapy for patients with ischemic stroke [55]. In addition, comparisons between telestroke and in-person evaluations have shown similar rates of stroke mimics, indicating that assessment scales and imaging interpretations are just as effective when conducted remotely [56]. Telestroke's acceptance across diverse cultures further underscores its effectiveness and potential for broader application. However, despite these strides in enhancing stroke care through telemedicine, there remains a gap in data regarding the suitability and practicality of telemedicine for treating other neurological conditions [57], highlighting an area ripe for exploration and development.

Another example is in neuromuscular conditions that encompass a wide range of disorders, from common diabetic neuropathy to rare diseases such as periodic paralysis. Many of these conditions, including amyotrophic lateral sclerosis (ALS), necessitate a comprehensive, multidisciplinary management approach. Despite rapid advancements in diagnostic technologies, the accurate diagnosis of many neuromuscular disorders often hinges on detailed neurological examinations to detect subtle clinical signs that might be overlooked in teleneurology assessments. However, telemedicine has been found beneficial for patients with established diagnoses and stable symptoms, offering a convenient option for follow-up evaluations [58]. Research on the use of teleneurology specifically for neuromuscular disorders is limited, and only a handful of studies have been published to date. These studies, primarily focused on patients with a confirmed diagnosis of ALS [55], revealed a generally positive perception of teleneurology among patients, caregivers, and health care providers. Patients expressed high levels of satisfaction appreciating particularly the elimination of travel-related burdens, which led to less stress and more comfortable medical interactions. In addition, a smaller study involving patients with advanced facioscapulohumeral muscular dystrophy indicated that teleneurology was well-received by both patients and caregivers [57]. The quality of care provided via teleneurology was rated highly in patient questionnaires, although it was noted that acute care issues were not addressed in these evaluations.

There are other examples such as concussions and traumatic brain injuries [59,60], dementia evaluations [61], and the management and follow-up of patients with epilepsy [62,63]. It has also facilitated the diagnosis and treatment of nonacute headaches [64-66], assessment of movement disorders [67-69], remote care for MS [70,71], as well as follow-up consultations and care management patients with neuromuscular diseases [52,72]. The COVID-19 pandemic saw an increase in telemedicine use across specialties to manage patient care during lockdowns, mask mandates, and overall minimization of personal interactions. This era is characterized by the adoption of telemedicine on a national scale, exemplified by Saudi Arabia's adoption of telemedicine as an alternative health delivery system [73] and the launch and deployment of a telemedicine program by the Italian government [74].

Improving Patient Flow and Early Detection

Stroke is a highly prevalent neurological disorder, affecting approximately 9.4 million Americans aged >20 years between 2017 and 2020 [75]. More than half of the patients who experienced stroke were left chronically disabled [76], and the annual mortality rate as of 2020 was 160,000 Americans [75]. For many years, stroke diagnosis was significantly hampered by time delays between the initial detection at radiologic centers and subsequent treatment at thrombectomy centers within hospitals. As of 2016, this delay averaged nearly 100 minutes in the United States, leading to increased morbidity [77] and disability [78]. In response to this challenge, an AI company developed a convolutional neural network (CNN) algorithm capable of automatically detecting ischemic stroke patterns associated with large vessel occlusions (LVOs) [79]. Upon identifying an LVO, the algorithm autonomously alerts the stroke treatment team, bypassing the need for any intervention by the clinician who requested the radiologic examination. Alerts are dispatched through a mobile app, facilitating immediate communication and resulting in an average reduction of 52 minutes in the time to LVO treatment initiation [80]. Beyond facilitating direct communication, modern AI-based telestroke systems enhance patient flow by autonomously analyzing radiological images, often surpassing the capabilities of human radiologists [81]. Clinical AI today is adept at interpreting CT and MRI scans to determine the size and extent of brain damage caused by ischemic strokes [81] and can even forecast the potential progression of the stroke [82].

AI has also augmented radiologist performance by aiding in the selection of patients for endovascular thrombectomy. This is achieved through the integration of automated Alberta Stroke Program Early CT Scores (ASPECTS) with clinical presentations, thereby correlating with the NIH Stroke Scale scores [83,84]. Moreover, AI proves its proficiency in acute prognosis prediction by evaluating detected infarct volumes [85] or white matter hyperintensities [86]. It even enables predicting treatment outcomes [84,87,88] with remarkable accuracy, including a notable 7% improvement in forecasting symptomatic intracerebral hemorrhage [89]. These advancements highlight AI's broad application in stroke care, from the analysis of radiological imaging to the identification of stroke indicators, enhancing intrahospital communication and significantly contributing to the decision-making process for timely and effective treatments.

Quantum Computing

Quantum computing represents the potential to change the way we view data storage, specifically in neurology. Unlike classical computers, which use bits to process information as binary 0s or 1s, quantum computers use qubits that can exist in multiple states simultaneously due to superposition. This allows quantum computers to process vast amounts of data at unprecedented speeds, making them exceptionally powerful for complex computations. Quantum computing could significantly enhance our ability to analyze large datasets, such as those generated from neuroimaging, genomics, and EHRs. The ability to process and analyze these massive datasets more efficiently can lead to more accurate models of brain function, disease progression, and treatment outcomes. For example, quantum algorithms could optimize machine learning models used for diagnosing neurological disorders, predicting disease trajectories, and personalizing treatment plans.

In summary, telemedicine and remote patient monitoring have emerged as transformative forces in neurological care, offering unprecedented access, convenience, and efficiency. From virtual consultations for stroke, neuromuscular disorders, and movement disorders to AI-driven early detection and prognostication in acute stroke management, these technologies are reshaping the landscape of neurological services. As we navigate the challenges posed by an aging population and a shortage of neurologists, the continued adoption and advancement of telemedicine hold immense promise in ensuring timely, equitable, and effective care for patients with neurological conditions worldwide.

Genetics and Omics: Driving Personalized Medicine in Neurology

Overview

The genetic and molecular insights gained from omics studies are informing the development of neurotechnological interventions, from brain-computer interfaces (BCIs) to neuroprosthetics (Figure 3). Despite the historical limitations imposed by the high costs of genetic analysis and the constrained ability to address neurological disorders once identified, recent technological advancements in DNA sequencing and gene editing have propelled genetic analysis and gene therapy to the forefront of clinical neurology. These innovations promise significant improvements in patient care, emphasizing the critical role of genetics in understanding and managing neurological diseases. The human genome's complexity, with its 3 billion nucleotides, of which <2% encode proteins, underlines the intricate relationship between genetic variations in both protein-coding genes and noncoding regulatory DNA and disease risk. Diseases can be monogenic, resulting from a single gene mutation, or polygenic, involving mutations across multiple genes. The advent of next-generation sequencing (NGS) has exponentially increased the speed, accuracy, and affordability of DNA sequencing, making it possible to use an individual's genome to guide their medical care. This leap in sequencing technology, alongside developments in gene editing, particularly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9, marks significant advancement toward correcting genetic mutations responsible for neurological diseases.

The integration of genomic information from genome-wide association studies (GWASs) for predicting disease risk and aiding in the identification of patient populations for clinical trials, points toward a future where genetic screening plays a crucial role in early intervention strategies. As gene-based diagnostics and treatments become more accessible and refined, the potential for addressing a vast array of neurological conditions grows, underscoring the importance of continued investment in basic science research to fuel the development of tomorrow's treatments.

Genetics in Predictive Analytics

Together, NGS and GWAS significantly enhance neurological predictive analytics by offering a comprehensive approach to understanding complex diseases. NGS provides detailed genetic screening and diagnosis, enabling precise prognostication, informed treatment planning, and accurate genetic counseling through genetic risk scores. It deepens our understanding of disease mechanisms by mapping phenotype or genotype correlations, paving the way for novel therapies and personalized medicine in neurology. GWAS, in turn, identifies genetic loci associated with various neurological conditions, illuminating their heritability and pathophysiology and revealing potential therapeutic targets. Collectively, these technologies form a potent toolkit for elucidating the genetic foundations of neurological disorders, promising advancements in treatment and patient care [90-92].

In the past 2 decades, GWAS facilitated many discoveries, such as the identification of multiple novel risk loci in neurodegenerative diseases like AD and PD (CR1, BIN1, and PICALM for AD [93]; SNCA and MAPT for PD [94]) that elucidate roles in lipid processing, the immune system, and synaptic-cell functioning pathways. Similarly, in ALS, GWAS findings have highlighted genes such as UNC13A and the significance of the 9p21.2 region in both familial and sporadic forms [95,96]. Chronic conditions such as MS [97], epilepsy [98], and restless legs syndrome [99] have benefited from GWAS revealing numerous loci, particularly highlighting the autoimmune nature of MS and the dopaminergic neurotransmission and iron dysregulation in restless legs syndrome. Cerebrovascular disorders, such as stroke [100] and Moyamoya disease [101], have revealed specific genetic risk factors through GWAS, including the identification of 8 different loci causing neurological instability postischemic stroke and the strong association of the RNF213 locus with Moyamoya disease risk. These discoveries underscore the complexity of neurological diseases and the crucial role of genetic factors, paving the way for targeted therapies and improved diagnostic strategies.

Genetic insights are instrumental for predictive models that use algorithms and statistical techniques, including machine learning and neural networks, to identify patterns and predict future clinical outcomes from data. For example, in neurovascular conditions such as cerebral aneurysms [102] and arteriovenous malformations [103], predictive models have successfully forecasted risks of cerebral aneurysm rupture and outcomes

following endovascular treatment of arteriovenous malformations. These predictions are based on a combination of basic demographics, clinical information, and computational blood flow simulations processed through machine learning and image processing techniques.

Beyond DNA sequencing, other "omics" have been transformative in various neurology traits. For instance, transcriptome analysis, used to measure the expression levels of genes, provided significant insights across various diseases. In AD, it uncovered 3 molecular subtypes [104] and led to the development of a blood RNA test that distinguishes AD from other dementias before symptom onset [105,106], also highlighting the downregulation of NeuroD6 as a potential biomarker [107]. For PD, it enabled patient stratification based on mitochondrial or lysosomal dysfunctions and assisted in selecting neuroprotective compounds [108]. In ALS, transcriptome analysis facilitated the molecular classification into 2 distinct subtypes, sporadic ALS group 1 and group 2, by analyzing deregulated genes and pathways in postmortem cortex transcriptomes [109,110]. Moreover, it revealed central nervous system (CNS) dysregulation of over 300 biological processes in prion infections and suggested alternative pathways for astrocyte activation [111]. It also identified molecular heterogeneity in trigeminal ganglia subregions, aiding in the understanding of migraine and headache mechanisms through the analysis of postmortem trigeminal ganglia [112]. Even though it was revolutionary at the time, bulk transcriptome analysis has several disadvantages that have prompted the development and adoption of single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics technologies. One key limitation of bulk transcriptomics is its inability to capture cellular heterogeneity within complex tissues or cell populations, as it provides only an average expression profile from a bulk sample. This averaging masks the diversity of individual cell types and their unique transcriptional states, which are crucial for understanding biological processes and disease mechanisms. In addition, bulk transcriptomics lacks spatial context, meaning that it cannot pinpoint where specific genes are being expressed in a tissue. scRNA-seq addresses these issues by profiling the transcriptomes of individual cells, revealing the cellular heterogeneity and enabling the identification of rare cell types and subpopulations. This detailed cellular landscape often yields valuable insights into disease progression, such as the discovery of key demyelinating subpopulations mediating early AD progression [113]. These discoveries are made possible and reliable due to large scRNA-seq databases, which can be either self-generated or obtained from publicly available repositories and atlases. The past decade has witnessed the emergence of many such atlases, including the Allen Brain Atlas [114], making it easier for researchers to conduct scRNA-seq analysis, as self-sequencing of data may be time-consuming and costly. Spatial transcriptomics technologies go a step further by retaining the spatial context of gene expression, allowing researchers to map where in a tissue each gene is active. Together, scRNA-seq and spatial transcriptomics offer a more detailed and nuanced view of gene expression.

Selective neuronal vulnerability as a subfield in neurology focuses on the molecular mechanisms underlying enhanced neuronal degeneration. This field highly benefited from single-cell technologies, which linked tau accumulation to AD progression and depletion of specific excitatory neurons [115]. In addition, these technologies enabled the identification of molecular features pruning degradation of dopaminergic neurons in PD [116]. Moreover, it facilitated the characterization of specific hippocampus and dorsolateral prefrontal cortex neuronal subtypes, involved in many neuropsychiatric disorders, such as schizophrenia and major depressive disorder [117]. Another neurology subfield highly benefiting from scRNA-seq-based discoveries is neuroimmune dysfunction, which sheds light on the function of immune cells in neurodegenerative disease progression. For example, studies have identified disease-associated microglia with unique gene expression profiles in AD models and distinct microglial responses associated with different stages of neurodegeneration [118,119]. In MS, transcriptomic analyses have uncovered microglial subtypes with specific gene dysregulations, suggesting potential therapeutic targets [120]. Furthermore, the adaptive immune response, involving T cells and B cells, has been implicated in the pathology of MS and PD, highlighting the influence of immune cells on neuronal degeneration [121,122]. Single-cell sequencing has also revealed key insights into glioma, showing how myeloid cell interactions within the tumor microenvironment drive disease progression and affect treatment outcomes [123]. Similarly, in COVID-19, it has identified changes in microglia and astrocytes gene expression, suggesting that inflammation and immune responses contribute to neurological symptoms, opening new paths for treatment [124]. Finally, single-cell technologies have also revolutionized the understanding of how different cell types within the CNS and tumors respond to treatments. In glioblastoma [125] and medulloblastoma [126], for instance, scRNA-seq has identified potential therapeutic targets based on the cells' developmental and inflammatory processes, demonstrating the potential for tailored treatments.

Despite significant advancements in the field, single-cell transcriptomics still faces challenges and limitations. These include technical hurdles in sample collection [127] and cell isolation from brain tissue [128,129], which impact data quality and reproducibility. Key future directions involve advancing single-cell multiomics to integrate various data types with clinical information, enhancing the precision of spatial transcriptomics and applying these technologies to brain organoids for deeper insights into brain function and pathology.

Neurotechnology: Advancing Diagnosis, Treatment, and Rehabilitation in Neurology

Overview

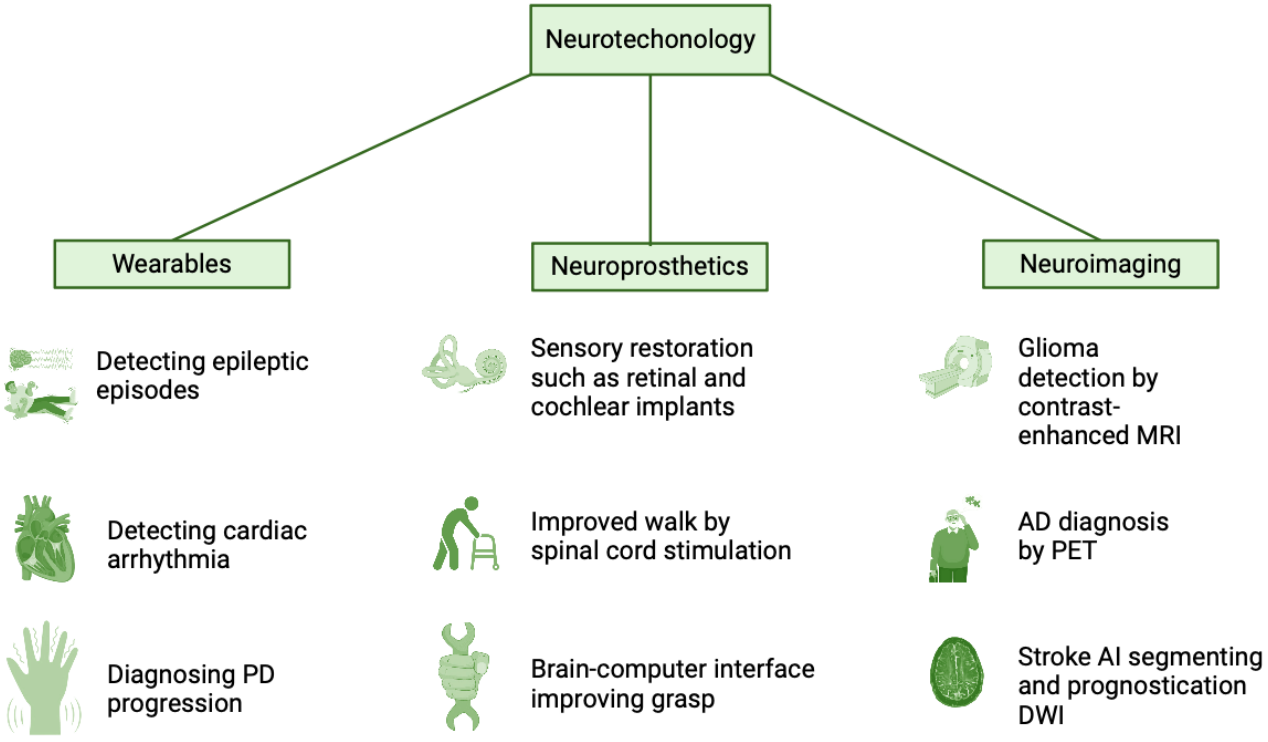
Neurotechnology refers to the integration of techniques and devices facilitating a direct interface between technical apparatuses and the nervous system (Figure 4). These technical components, including electrodes, computers, or advanced prostheses, serve the purpose of capturing signals from the brain and converting them into operational commands or modulating brain activity through the application of electrical or optical

stimuli. Ongoing research explores closed-loop interactions between systems for signal acquisition and stimulation (control circuits) [130].

Neurotechnology has its roots in the early exploration of brain electrical activity. Electrical currents of the brain were first described in 1875 by Richard Caton, who observed electroencephalography from exposed rabbits' and monkeys' brains. In 1924, German neurologist Hans Berger enhanced the measurement of human brain electrical activity through the scalp, recording and depicting it graphically on paper. This laid the foundation for modern EEG technology, which has become a cornerstone of noninvasive BCIs. EEG signals are now commonly used in BCIs to facilitate bidirectional communication between the human brain and external devices. By monitoring various cortical regions, it is possible to extract signals across multiple frequency bands associated with distinct human behaviors, enabling the study of corresponding patterns. EEG-based BCIs have significantly advanced our understanding of cognitive activities and contributed to progress in computer science and engineering [131]. In EEG-based BCI applications, machine learning technologies typically fall into 2 major categories: classification and individual adaptive tasks. Deep learning, a subset of machine learning, uses deep neural networks to learn EEG patterns [132], featuring numerous neurons across multiple layers to capture cognitive-related features. The potential of BCIs is particularly evident in the field of robotics. EEG-based BCIs have demonstrated efficacy in communication with robots, with early applications, including the control of wheelchairs through visual simulations or motor imagery [131]. These advancements pave the way for more sophisticated neurotechnological interventions in movement, language, and speech, as we will explore in the subsequent sections.

In summary, as neuroprosthetics involves devices that interact directly with the nervous system to restore or enhance neural functions and BCIs enable direct communication between the brain and external devices, they can bypass traditional pathways. They typically rely on electrodes that capture electrical signals from the brain or stimulate neural tissue. These electrodes can be noninvasive, which are placed on the scalp, or invasive, which are implanted directly into the brain. BCIs decode neural signals into commands that control prosthetic limbs, computers, or other devices, often using machine learning algorithms to interpret complex brain activity. There are a few technical challenges such as ensuring long-term biocompatibility and stability to prevent immune responses and device degradation. The integration of neurotechnology into clinical practice requires extensive training for both patients and health care providers. Patients must learn to use and control neuroprosthetic devices effectively, which often involves cognitive and physical training. Health care providers need specialized knowledge to implant, configure, and maintain these devices, as well as to provide ongoing support and adjustments based on patient needs.

Figure 4. Summary of neurotechnology advances in the last half-century. AD: Alzheimer disease; AI: artificial intelligence; DWI: diffusion-weighted imaging; MRI: magnetic resonance imaging; PD: Parkinson disease; PET: positron emission tomography.



Aiding Movement Language and Speech

One example is electrodes that are capable of noninvasively capturing electrical fields generated by the active brain, typically facilitated by their placement on the surface of the head in the form of electrode caps. This method is deemed noninvasive as the electrodes do not penetrate body tissues. Notably, it finds application in patients afflicted with ALS, particularly during the advanced, near-complete paralysis stages where it aids speech by synthesizing it real time directly from brain activity

[133]. For instance, electrodes used for deep brain stimulation (DBS) are meticulously inserted by neurosurgeons into targeted brain regions. Through modulation of these targets, it becomes feasible to suppress or ameliorate certain symptoms associated with various brain disorders. For instance, DBS serves as a therapeutic option for patients with PD when conventional medication proves ineffective. While DBS does not offer a cure or halt the progression of neurodegenerative processes, it substantially alleviates hallmark symptoms such as tremors or rigidity, thereby significantly enhancing patient well-being and overall quality of life [130].

Neurological Wearables

Another illustration within the realm of neurotechnology pertains to neurological wearables. A primary challenge concerning wearable sensors revolves around creating stretchable and skin-attachable electronic devices capable of seamlessly and inconspicuously monitoring human activity and vital signs without impeding or restricting the user's movement [134]. The initial breakthrough in implantable medical devices came with the development of a pacemaker for patients with arrhythmia in 1958 [135]. Since this milestone, a range of pacemakers and implantable cerebellar stimulators have been developed and used [134].

In neurology, wearable devices are considered an evolving technology used to track and monitor the patient's ambulatory status for long periods. It can track vital signs and other types of data, creating a digital profile of the patient [136], even during their sleep. The collected data are expected to improve the diagnosis, assessment, and treatment of patients with various conditions. Out of the health care companies investing in the development of wearable devices, around 60% were founded after 2006, whereas the oldest one was founded in 1993 [137]. Many wearable devices were developed to diagnose, monitor, and treat neurological disorders, such as stroke, PD, and epilepsy. In stroke, smartphones and smartwatches are primarily used to monitor parameters, such as upper extremity activity, walking, and physical activity [138], all of which may detect pulse and cardiac arrhythmia [139] that can cause subsequent transient ischemic attacks or ischemic strokes [140]. In PD, wearable devices in the form of sensors attached to the lower back may track cardinal motor symptoms, such as postural sway, tremor and bradykinesia, quantity and duration of freezing and falling phases, sleeping distributions, and also more cognitively advanced symptoms like dyskinesia [138]. In epilepsy, most wearables are wrist-worn sensors with accelerometers, which are used to identify seizures based on movement patterns that might be associated with tonic-clonic or convulsive seizures [138].

One example of such a device is the Embrace smartwatch, which quantifies alterations in skin electric conductance that correspond to epileptic activity within the brain, and it can notify contacts or caregivers about the seizure activity it identified [141]. Other such devices include one that had electrodes attached to the biceps and detected tonic-clonic seizures and another that detected simple partial seizures [141].

An additional instance pertains to the use of wearables within the realm of sleep neurology. The neurological status of patients is notably influenced by both the quality and quantity of sleep. Wrist-worn actimetry sensors have been established as longstanding tools in sleep studies, enabling the monitoring of various physiological parameters associated with sleep [140]. These devices may be supplemented by cardiac monitoring or mattress-based devices, colloquially termed "nearables," which possess the capability to track respiratory movements [142]. Several newer devices actively intervene with the patient's sleep, helping them to get better sleep quality [140].

In all the mentioned wearables, AI technologies play a crucial role in their embedded architecture, as they enable the mass analysis and process of the detected data. However, efficient AI tools or wearables require large amounts of training data, effective noise removal from detected features, and subsequent feature selection (ie, focusing on important data characteristics for each type of evaluation). Furthermore, it involves distinguishing between similar activities and developing computationally efficient algorithms and hardware implementations. Nevertheless, there are significant technical challenges such as the need for energy-efficient designs to ensure long battery life, robust data privacy and security measures, and overcoming the devices' limitations of real-time data processing. Addressing these challenges is essential for the successful deployment and widespread adoption of AI-enabled neurological wearables [143,144].

Despite its ongoing popularity and contribution to patient care, there are some current issues with wearables in the field of neurology. These mainly include a lack of high-quality data, an absence of accepted evaluation standards, and limited implementation strategies; many wearables lack robust efficacy data that would improve the care of abundant disabling neuropsychiatric conditions, such as migraine and depression [140]. As for evaluation standards, even though the American Psychiatric Association proposed a framework for evaluating digital health tools in 2018 [145], there is still no widely accepted standard [146]. This lack of standards results in inconsistent evaluations and limits implementations. Apart from evaluation problems, the rapid development of wearables also outpaces the creation of validation protocols, resulting in a lag in adapting these tools to health care systems [140].

Robotics in Neurological Diseases

Researchers have discovered that robotic devices significantly enhance stroke rehabilitation by offering patients tailored, intensive, and repetitive training. These devices facilitate real-time feedback, enabling immediate correction of movement errors, thus fostering more efficient and effective motor learning. With the ability to provide targeted training, these robots not only enhance motor learning but also deliver objective performance and function measurements. Customizable to individual patient needs, these robotic systems can be programmed for specific training or therapeutic interventions, underscoring their versatility in rehabilitation [147]. Neural rehabilitation is an emerging field aiming to restore defective neurological circuits' functionality or enhance the remaining functionality of impaired ones. Its purpose is to enhance patient's independence and improve their quality of life by relying on the principle of neuroplasticity [148,149], a subject

that relies on the idea that CNSs and peripheral nervous systems can be retrained after an injury to achieve an effective rehabilitation [150]. Another application is in pediatric neurosurgery; robot-assisted stereotactic biopsies for brainstem and thalamic lesions have proven effective, showcasing the potential of robotic procedures in enhancing surgical precision and accuracy and minimizing tissue damage. This approach has been particularly promising in pediatric neurosurgery, offering a method to improve outcomes while reducing the risk to surrounding healthy tissues [147].

Robotics is also making strides in the clinical assessment of neurological disorders and upper-limb therapy, indicating a broader application of this technology beyond traditional settings. Investigations into robot-assisted diagnosis and the use of robotic control through neural interfaces for individuals with tetraplegia highlight the innovative applications of robotics in neurology and intensive care.

Human-robot interaction is an emerging field that integrates AI, robotics, and social sciences to facilitate interaction and communication between humans and robots. It has various applications in medicine and also specifically in neurorehabilitation [151,152]. When using robots, numerous considerations must be considered, including safety, learning by demonstration, imitation learning, cognition and reasoning, perception, and more [153]. Typically, AI algorithms and systems are used to address these issues, thereby enhancing the overall interaction and experience for patients. Owing to the presence of multiple representations within an environment, there is often an abundance of multimodal data, such as visual, audio, infrared, and ultrasound inputs. These inputs are used by AI algorithms capable of conducting tasks, such as object classification, prediction, and task planning [154].

Neuroprosthetics

Neuroprosthetics is an evolving field that combines neuroscience, engineering, and medicine to develop devices that can restore or enhance neural function. These devices, known as neuroprostheses, interact directly with the nervous tissue, usually to bridge the gap between lost function and the brain's control over the body. Over the past 25 years, several key advancements have propelled the field of neuroprosthetics forward. Notable examples of these advancements are BCIs, which have emerged as a promising avenue for restoring communication and control in patients with severe motor impairments. Notable achievements include the development of high-performance BCIs that enable users to control prosthetic limbs with near-natural dexterity and speed. One example of such achievement is a description of 2 patients with spinal cord injury who were able to regain their grasp function through neuroprosthesis, by using an asynchronous BCI, allowing them to complete a Grasp and Release Test of the paperweight multiple times [155].

Another example is advancements in sensory restoration. Neuroprosthetics has made significant progress in restoring sensory function, particularly in the realm of hearing and vision. Cochlear implants, which aid more than half a million people worldwide with severe to profound hearing impairment [156], electrically stimulate the auditory nerve to restore hearing and have become increasingly sophisticated, offering improved sound quality and speech recognition. Recently, a demonstration of a new development in the cochlear implant field was presented, allowing better pitch perception for the users by using haptic stimulation on the forearm [156]. Similarly, retinal implants and optogenetic approaches have shown promise in restoring visual perception in individuals with blindness, as can be seen from the launching of 2 electrical retinal prostheses in the last 2 decades, as well as preclinical and early clinical trials of gene therapies in the field of optogenetics [157].

Neuroprosthetic devices have also been developed to stimulate the spinal cord, offering new treatment options for individuals with spinal cord injuries or neurological disorders. These devices can modulate neural activity in the spinal cord, leading to improved motor function, reduced spasticity, and enhanced sensory feedback. Recent studies have demonstrated the potential of spinal cord stimulation to restore voluntary movement in patients with paraplegia. Another demonstration is of functional electrical stimulation electrodes that help patients with improper trunk stabilization due to spinal cord injuries by stimulating lumbar erector spinae among other muscles, improving their posture and forward reach and easing their transfers [158,159]. Furthermore, epidural spinal cord stimulation has been proven to activate central pattern generator for locomotion, thus improving walking in patients with incomplete spinal cord injuries [160].

Neuroprosthetics have led to the development of closed-loop systems that can sense and respond to neural activity in real time. These systems incorporate feedback mechanisms that allow the device to adapt its stimulation parameters based on the user's needs and intentions. Closed-loop neuroprosthetics have shown promise in applications, such as tremor suppression in PD and seizure detection and intervention in epilepsy. A neurotechnology company created a closed-loop stimulation device that can detect and prevent seizures from 4 channels [161], by comparing preseizure parameters to predefined thresholds, by both cortical and deep-brain stimulation. It also reduced sudden unexpected death in epilepsy significantly [162]. Another company developed a closed-loop device for PD treatment that can record focal deep-brain potentials and accordingly adjust the stimulation amplitude and frequency [163].

Finally, neuroprosthetic devices have become increasingly miniaturized and wireless, improving their implantability and reducing the risk of complications. Wireless power transfer and data communication have enabled the development of fully implantable systems that can operate without the need for external hardware. These advances have greatly enhanced the practicality and acceptability of neuroprosthetic devices for long-term use. One example of miniaturized neuroprosthetics is cochlear implants, which use small electrodes with small diameter wires of 20 µm [164] and an electrode array that is considered one of the longest is only 31.5 mm [165]. Another example of a miniaturized and wireless device is an endovascular, wireless, and battery-free millimetric implant that can stimulate specific peripheral nerves that are difficult to reach surgically [166].

Despite these advancements, challenges remain in the field of neuroprosthetics. These include ensuring the long-term stability and biocompatibility of implanted devices, optimizing the specificity and resolution of neural interfaces, and developing more intuitive control strategies for users. In addition, translating neuroprosthetic technologies from research settings to clinical practice requires rigorous testing, regulatory approval, and consideration of ethical and social implications.

Looking ahead, the field of neuroprosthetics holds immense promise for improving the lives of individuals with neurological disorders or injuries. Ongoing research aims to further enhance the functionality and usability of neuroprosthetic devices, incorporating advancements in materials science, machine learning, and neuroscience. As these technologies continue to evolve, they have the potential to revolutionize the way we approach neurological rehabilitation and restoration of function.

Advancements in Neuroimaging: Transforming Neurosurgery, Neuro-Oncology and Stroke Care

Overview

As we look forward to breakthroughs in neuroprosthetics, advancements in neuroimaging are equally revolutionizing the field of neurological diagnostics and treatments. The advent of new imaging techniques like CT, nuclear magnetic resonance, PET, and ultrasonic scanning has revolutionized our understanding of the nervous system in both its healthy state and when affected by the disease (Figure 4). These advancements have provided unprecedented clarity and detail in imaging, greatly enhancing our diagnostic capabilities.

Neuro-Oncology and Neurosurgery

Innovations in neuroimaging have been pivotal in enhancing patient care, significantly reducing morbidity and mortality rates among patients receiving neurosurgical care [167]. The improvement in brain MRI for anatomical mapping has led to rapid growth and progress. This enhancement is important for diagnosing and treating oncological diseases of the nervous system, which include a variety of tumors such as meningiomas. Among the most prevalent primary brain tumors in adults are cerebral gliomas, with an incidence rate of 5 to 6 per 100,000 person-years [168]. At the point of initial diagnosis, the challenge of distinguishing brain tumors from benign lesions is challenging due to their similar appearances on MRI scans. Contrast-enhanced MRI, favored for its superior soft-tissue resolution and accessibility, serves as the primary method for such differentiation. Typically, brain tumor diagnoses rely on conventional MRI techniques, including T1-weighted and T2-weighted sequences. However, these standard imaging approaches sometimes struggle to distinguish between tumor changes due to disease progression and nonspecific, treatment-related alterations, especially after therapeutic interventions. PET scanning, using various radioactive tracers to target distinct metabolic and molecular processes, offers more data that enhance specificity, especially in clinically ambiguous cases. Radiolabeled amino acids in PET scanning become essential in neurodiagnostics, with the Response Assessment in Neuro-Oncology working group recommending its use alongside MRI for comprehensive brain tumor management. Meanwhile, advanced MRI techniques like perfusion-weighted imaging, diffusion-weighted imaging (DWI), and proton magnetic resonance spectroscopic imaging [87] continue to be evaluated clinically for their potential to provide critical physiological or biochemical insights beyond standard MRI capabilities. The evolution of modern neurosurgery and radiology demonstrates the impact of radiological advancements on neurosurgical practices. The pace of these developments is so rapid that newer neurosurgical residents might be unfamiliar with older procedures like pneumoencephalography or the challenges of distinguishing between neurosurgical pathologies before the advent of CT. Moreover, such progress has supported the execution of high-quality clinical trials, improving evidence-based neurosurgical practice.

Stroke Medicine

Stroke is one of the leading causes of death in older ages and time to treatment is crucial. Over the recent decades, ischemic stroke medicine has evolved with new technological innovations, specifically with the advent of AI and the few critical examples mentioned subsequently are just the tip of the iceberg. Multiple AI-based models are able to detect and segment core infarct, detect LVO, calculate ASPECTS score, and more [169]. One example is a study from 2011, in which a computer-automated detection (CAD) scheme using a circular adaptive region of interest method was developed and implemented on noncontract head CT scans to identify subtle changes in attenuation indicative of ischemic stroke [170]. The findings from the study indicated that CAD significantly enhanced the detection of strokes for emergency physicians and radiology residents [170]. In another study, researchers demonstrated the efficacy of an artificial neural network in distinguishing acute strokes from stroke mimics within 4.5 hours of symptom onset, with a mean sensitivity of 80% and specificity of 86.2% [171]. In the domain of automatic lesion segmentation, a recent study used an ensemble of 2 CNNs to effectively segment DWI lesions, irrespective of their size, while simultaneously mitigating false positives, achieving a Dice score of 0.61 for small lesions and 0.83 for large lesions [172]. In detecting LVOs, a support vector machine (SVM) algorithm demonstrated high sensitivity (97.5%) in identifying the Middle cerebral artery dot sign on noncontrast CT scans in patients with an acute stroke [173]. A commercial software, based on CNN, achieved an accuracy of 86% in detecting proximal LVO, with a sensitivity of 90.1% and specificity of 82.5% [174]. In ASPECTS grading, a commercial software platform offering automated ASPECTS scoring demonstrated comparable performance to neuroradiologists in scoring ASPECTS on noncontrast CT scans in patients with acute stroke (P<.003) [175]. In stroke prognosis, a study found that a generalized linear model combining DWI and perfusion-weighted imaging MR outperformed individual modalities in predicting tissue outcomes [176], and another study showed that a CNN trained on MRP source images achieved an area under the curve of 0.871 in predicting final infarct volume [177].

Neurodegenerative Diseases

The significance of biomarkers in comprehending and diagnosing neurodegenerative diseases is growing. The use of imaging biomarkers for the live examination of these disorders has seen a significant rise in recent decades, offering enhanced diagnostic capabilities and deeper insights into disease mechanisms.

Neurodegenerative diseases, notably AD, are understood to commence years before the manifestation of symptoms. Research, particularly on familial AD, outlines a sequence of pathological events beginning with the buildup of amyloid beta (Aβ), detectable via PET imaging and cerebrospinal fluid analysis, culminating in cognitive deficits and dementia. These processes not only occur in a specific sequence but also overlap over time, offering insights into the disease's progression. The National Institute on Aging and Alzheimer's Association has established a research framework for AD diagnosis, using the AT(N) scale to categorize Aβ, tau, and neurodegeneration markers. These markers, identifiable through imaging biomarkers in vivo, enhance the sensitivity and specificity of AD diagnostics, underscoring the vital role of advanced imaging techniques in the early detection and understanding of neurodegenerative diseases. Neuroimaging has become integral to diagnosing suspected neurodegenerative diseases, using various MRI techniques, and developing novel PET ligands. These tools provide objective measures for detecting and monitoring disease presence and progression, aiding in patient care, and facilitating clinical trial recruitment and treatment efficacy evaluation. The cross-disciplinary approach, incorporating imaging biomarkers, is crucial for diagnosing and comprehending neurodegenerative disorders, emphasizing the expanding utility of neuroimaging in medical research and patient management [178]. Aβ PET imaging has transformed the diagnostic landscape for AD, allowing for the in vivo quantification of Aβ plaques, a key AD biomarker. The development of Aβ-specific PET tracers, such as Pittsburgh compound B and subsequent F-18-labeled tracers, has facilitated this advancement [179]. Similarly, tau-specific PET tracers have opened new avenues for diagnosis, prognosis, and clinical trial outcomes in AD, correlating tau pathology with cognitive symptoms and deterioration [180]. The portfolio of PET ligands for identifying biomarkers of neurodegeneration has grown considerably, with some advancing to clinical use and others offering new insights into these conditions. MRI techniques continue to aid diagnosis and enhance our understanding of neurodegenerative diseases, with structural MRI being the most accessible imaging tool. Fluorodeoxyglucose PET, despite its limitations, remains a valuable tool for investigating neuronal injury in dementia [181], illustrating the complex nature of neuroimaging in understanding and treating neurodegenerative diseases.

Few studies also use machine learning to aid diagnosis. For example, an innovative CAD system was developed to diagnose AD from MRI images, based on aging brains and machine learning, and to identify the AD-related regions [182]. The experiments demonstrated that the proposed method could predict AD patients with a competitive accuracy of 92.36%, comparable to existing methods. In another study, the researchers trained a deep learning algorithm based on CNN to predict a diagnosis of AD or mild cognitive impairment, based on fluorodeoxyglucose-PET imaging [183]. The algorithm achieved an impressive area under the receiver operating characteristic curve of 0.98 when predicting the final clinical diagnosis of AD in an independent test set. It demonstrated 82% specificity at 100% sensitivity, with predictions made an average of 75.8 months before the final diagnosis. Notably, the algorithm's performance surpassed that of human readers, with a sensitivity of 57% and specificity of 91%. Saliency map analysis revealed an attention to known areas of interest, highlighting the entire brain's importance in the diagnostic process [183]. Another example is PD, a common neurodegenerative disease where early detection is highly important to improve patient's quality of life [184]. In recent years, remarkable progress has been made in using advanced computational methods in neuroimaging, providing a valuable tool set for the medical imaging research community to extract pertinent features. These methodologies have been instrumental in developing sophisticated diagnostic approaches for PD [184]. In one study neural activity and functional connectivity within the olfactory brain network were investigated [181]. Through the application of independent component analysis and the generalized linear model, discernible differences between patients with PD and healthy controls were identified, with independent component analysis demonstrating superior performance compared with generalized linear model. Similarly, a predictive model using fMRI datasets for PD diagnosis through multiclass patient classification was devised [182]. Feature reduction and selection were achieved using principal-component analysis and the Fisher discriminant ratio, while the classification task was carried out using the least square SVM. Notably, these classifiers exhibited impressive accuracy levels of up to 87.89% and a precision of 82.54%. In another study, resting-state fMRI datasets were used, leveraging an SVM classifier to effectively distinguish 19 patients with PD from 18 healthy controls [183]. In a study aimed at building a model based on Grey's cerebellum changes, an SVM classifier used data of cerebellar structural changes derived from voxel-based morphometry for PD detection with an accuracy of more than 95% [184]. Researchers also reported that they were able to detect and differentiate successfully patients with PD from healthy ones, by associating different facial expressions and brain activity on fMRI.

In conclusion, the field of medical imaging has witnessed remarkable progress, evolving from the inception of x-ray imaging to the advent of fMRI and other cutting-edge technologies. This trajectory of innovation, coupled with the emergence of AI technologies, has paved the way for groundbreaking applications in the realm of neurological disorders, significantly enhancing our understanding of various neurological conditions.

Summary

The integration of AI with new medical technological advancements has ushered in a transformative era for neurology, reshaping diagnostic, therapeutic, and research landscapes. With the advent of EHR systems and the widespread adoption of

telemedicine, neurologists now have unparalleled access to patient data and the ability to deliver care remotely. This shift streamlines clinical workflows and enhances patient care by enabling precise and timely interventions. As most neurological conditions are chronic and require monitoring, this advancement allows for scaling in treatment. Furthermore, the burgeoning field of predictive modeling, powered by vast databases of EHRs, leverages AI to forecast clinical outcomes, offering personalized treatment strategies.

The paradigm shift from traditional physical examinations to reliance on technological data has significantly impacted patient triage and clinical management. Innovations, such as advanced imaging technologies, revolutionized neurological diagnostics, providing deep insights into the brain's anatomy and function. Stroke prevalence led to the dire need for rehabilitation in neurology, while new wearable devices and robotics in rehabilitation have further expanded the horizons of patient care, offering targeted therapy that adapts to the dynamic needs of individuals and saves expensive hospital visits. These technological advancements highlight the evolving approach to neurology, emphasizing the importance of integrating cutting-edge tools for improved diagnosis, treatment, and patient outcomes. AI models that analyze brain imaging to detect strokes, coupled with predictive models for conditions like ALS and AD, demonstrate the potential of machine learning to improve patient care and bring to fruition personalized medicine in neurology. The collaboration between neurology and AI technologies paves the way for breakthroughs in understanding and treating neurological disorders, marking a significant leap toward advancing neuroscientific research.

Limitations are present across all these transformative ideas, particularly in advanced imaging technologies such as fMRI, PET, and CT, where challenges include cost, accessibility, and resolution constraints. Another example of the limitations is AI algorithms and their potential biases or hallucinations, data requirements, and the challenges in integrating those into clinical practice or ensuring patient privacy. In genomics, the issues are ethical concerns, off-target effects, the high cost of these technologies, and more.

In summary, the intersection of neurology with emerging technologies has fundamentally changed the landscape of neurological practice. From enhancing diagnostic accuracy and streamlining patient care to personalizing treatment strategies, the entire neurology field stands at the forefront of this revolution. The integration of AI, advanced imaging, and telemedicine underscores its dynamic evolution, driven by the pursuit of excellence in patient care and neuroscientific discovery.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADNI: Alzheimer's Disease Neuroimaging Initiative
AI: artificial intelligence
ALS: amyotrophic lateral sclerosis
ASPECTS: Alberta Stroke Program Early CT Scores
Aβ: amyloid beta
BCI: brain-computer interface
CAD: computer-automated detection
CNN: convolutional neural network
CNS: central nervous system
CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
CT: computed tomography
DBS: deep brain stimulation
DWI: diffusion-weighted imaging
EEG: electroencephalogram
EHR: electronic health record
fMRI: functional magnetic resonance imaging
GWAS: genome-wide association study
IMNM: immune-mediated necrotizing myopathy
LVO: large vessel occlusion
MRI: magnetic resonance imaging
MS: multiple sclerosis
NGS: next-generation sequencing
NIH: National Institutes of Health
PD: Parkinson disease
PET: positron emission tomography
scRNA-seq: single-cell RNA sequencing
SeLECT: severity of the stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery
SVM: support vector machine

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Original Paper

Assessing the Role of the Autonomic Nervous System as a Driver of Sleep Quality in Patients With Multiple Sclerosis: Observation Study

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Abstract

Background: Low sleep quality is a common symptom of multiple sclerosis (MS) and substantially decreases patients' quality of life. The autonomic nervous system (ANS) is crucial to healthy sleep, and the transition from wake to sleep produces the largest shift in autonomic activity we experience every day. For patients with MS, the ANS is often impaired. The relationship between the ANS and perceived sleep quality in patients with MS remains elusive.

Objective: In this study, we aim to quantify the impact of the ANS and MS on perceived sleep quality.

Methods: We monitored 77 participants over 2 weeks using an arm-worn wearable sensor and a custom smartphone app. Besides recording daily perceived sleep quality, we continuously recorded participants' heart rate (HR) and HR variability on a per-second basis, as well as stress, activity, and the weather (20,700 hours of sensor data).

Results: During sleep, we found that reduced HR variability and increased motion led to lower perceived sleep quality in patients with MS (n=53) as well as the age- and gender-matched control group (n=24). An activated stress response (high sympathetic activity and low parasympathetic activity) while asleep resulted in lower perceived sleep quality. For patients with MS, an activated stress response while asleep reduced perceived sleep quality more heavily than in the control group. Similarly, the effect of increased stress levels throughout the day is particularly severe for patients with MS. For patients with MS, we found that stress correlated negatively with minimal observed HR while asleep and might even affect their daily routine. We found that patients with MS with more severe impairments generally recorded lower perceived sleep quality than patients with MS with less severe disease progression.

Conclusions: For patients with MS, stress throughout the day and an activated stress response while asleep play a crucial role in determining sleep quality, whereas this is less important for healthy individuals. Besides ensuring an adequate sleep duration, patients with MS might thus work to reduce stressors, which seem to have a particularly negative effect on sleep quality. Generally, however, sleep quality decreases with MS disease progression.

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KEYWORDS

sleep quality; multiple sclerosis; autonomic nervous system; wearable sensors; mobile phone

Introduction

Low sleep quality can lead to decreased mental and physical performance [1,2] and thus impacts quality of life. The autonomic nervous system (ANS) indirectly affects sleep because it regulates different physiological processes within the human body that affect the way we sleep, for example, respiration and heart rate (HR). The relation of the ANS to sleep quality is not well studied for diseases that are explicitly known to affect the ANS, such as multiple sclerosis (MS) [3], Parkinson disease [4,5], or Alzheimer disease [6,7].

For patients with MS, sleep quality is one of the main drivers for quality of life [8-11] besides disability, depressive mood, and fatigue. Sleep quality is often reduced in patients with MS due to cramps, pain, reduced mobility, spasticity, mucus retention, and restless leg syndrome [12]. Reduced sleep quality has been shown to increase the level of proinflammatory cytokines, which can result in a general worsening of symptoms (eg, fatigue or pain) [11]. Higher sleep quality has been linked to reductions in MS-related (secondary) fatigue [13,14].

Patients with MS are often affected by a dysfunction of the ANS [15]. Patients with MS have increased chances of observing symptoms of a dysfunctional ANS as early as 10 years before their diagnosis, indicating an early involvement of the ANS in disease progression [16].

HR variability (HRV) is considered a noninvasive measure for the activity of the ANS, for which it is one of the main biomarkers [17]. Owing to the evolution of mobile devices, such as smartwatches and fitness wristbands, their users can now reliably and continuously track HRV as well as other vital signs [18]. It is, therefore, possible to assess sleep quality using continuous data streams in real-life settings outside of sleep laboratories [19,20].

While laboratory-based polysomnography is still the gold standard of analyzing how humans behave while asleep [21,22], assessing sleep quality using continuous data streams in a real-life setting has many advantages. Using a vital tracker worn on the wrist, for instance, data can be recorded without great effort from the participants [21]. Studies can, thus, run for longer periods and unlock new data sources recorded outside sleep laboratories (eg, HR or step count during the day). The information acquired outside sleep laboratories using wearable sensors is more precise at a more granular level [23] than what can be assessed through questionnaires such as the Pittsburgh Sleep Quality Index [24].

In this study, we investigate how the activity of the ANS affects perceived sleep quality for patients with MS as well as a control group by constructing predictive models for subjective sleep quality based on continuous data streams collected over 2 weeks using a wearable sensor and a smartphone app. We thereby extend past studies that have investigated how HRV changes during sleep [18-20,25], how sleep quality (subjective and objective) is affected by factors such as stress [26-28], and how the ANS and HRV are affected by sleep disorders [29,30] and diseases such as MS [3,18,31]. In addition, we analyze the trade-off in performance between explainable and interpretable modeling techniques such as logistic regression and less easily interpretable techniques when modeling subjective response data. Techniques that are harder to interpret than logistic regression (eg, support vector machines, neural networks, or boosted decision trees) have been found to often outperform generalized linear models (GLMs) on medical data [32-34]. However, these methods are closer to so-called black box methods that are neither easily interpreted nor explained and have to be treated carefully when used for medical application [35].

Methods

Participants

For this study, patients diagnosed with MS aged between 18 and 65 years without concomitant diseases were recruited by convenience sampling at the neuroimmunology department outpatient clinic of the University Hospital Zurich, Switzerland. Patients with MS (n=53) and a control group (n=24) were recruited between November 29, 2019, and July 29, 2021. On average, participants were aged 35.8 (SD 10.1) years, and 48 participants were female. We ensured that for each patient with MS, there was at least 1 member of the control group with the same sex and within –5 to + 5 years of age. Overall, we tried to ensure a similar age distribution and sex ratio between the control group and patients with MS. As confirmed by Wilcoxon signed rank tests (Mann-Whitney *U* tests) post hoc, there is no significant difference in age or sex ratio between the 2 groups. With an average age of 36.8 years patients with MS are on average more than 3 years older than participants of the control group (33.5 years) corresponding to a *P* value of .11. In total, 35 out of 53 patients with MS are female compared to 13 out of 22 participants of the control group. The *P* value for differences in the sex ratio is 0.33.

In total, 2 patients with MS (not included in the count of 53) aborted the study. One patient aborted the study because of a medical emergency requiring stationary medical treatment. The other patient aborted the study because of feeling overwhelmed by the study procedure. Otherwise, all participants adhered to the study protocol.

We based our study size on the general recommendations for feasibility studies, which recommend numbers of 24 to 50 patients with MS [36-38]. We confirmed these estimates when determining the study size based on the precision of compliance rate estimates. Given the short duration of the study, we expected high compliance rates of >85%. We calculated that we would be able to estimate a participation rate as low as 85% to within –10% to +10% at a 95% CI based on a sample size as small as 49. Hence, we recruited via convenience sampling and aimed for at least 49 patients with MS. The high compliance rate was later confirmed with only 2 patients with MS aborting the study.

We included information about the medication of patients with MS in Multimedia Appendices 1 and 2. In particular, we listed medication that is known to affect HRV metrics and disease-modifying treatment (DMT).

Ethical Considerations

The study protocol was reviewed and approved by the Cantonal Ethics Committee of Zurich (SNCTP000003494). All participants gave written informed consent, and procedures were in compliance with the Declaration of Helsinki.

Data Set Description

For 2 weeks, the participants wore a wearable sensor on the arm (Everion, Biofourmis AG) to continuously record their HR, HRV, step count, and motion data from the arm. To ensure continuous data recording, participants were equipped with 2 Everion sensors. The Everion records HR and the total magnitude from a 3-axis accelerometer at 1 Hz as well as interbeat intervals (IBIs). We processed the raw IBIs identifying artifacts as proposed by Berntson et al [39]. We linearly interpolated all missing IBIs and chunked the continuous data stream into nonoverlapping 5-minute windows. We removed any 5-minute window with ≥5 interpolated IBIs. For all remaining 5-minute windows, we calculated the SD of the distance from the 45° line of the Poincaré plot of consecutive IBIs (SD1), the SD of the distance from the –45° line of the Poincaré plot of consecutive IBIs (SD2), and the SD of IBIs (SDNN).

Through a custom-developed smartphone app, participants logged their sleep quality each morning after waking up (Textbox 1) and stress levels continually during the day over the course of the 2 weeks. Participants logged their level of stress on a scale from 1 to 10. Participants received daily reminders to rate their quality of sleep and stress levels. We collected information about outside temperatures using an application programming interface service [40]. We equipped participants with a Google Pixel 3 (Google LLC) for the duration of the study in case their phone was not suitable to install our smartphone app (eg, they had an iPhone).

The continuous data streams (HR, HRV, motion, and step count) were aggregated per day depending on whether the participants were awake or asleep, extracting the average, minimum, and maximum (Table 1). In addition to these resulting nonstatic variables, which change on a day-to-day basis, we collected demographic information of each participant. For patients with MS, information about disease state, severity of MS-related disability, functionality of the ANS, and affection of the spinal cord was also collected. We modeled daily perceived sleep quality recorded each morning using nonstatic variables collected since the participants last woke up the previous day.

After the completion of the study, deidentifiable data were stored on secure, password-protected servers. The data are only shared with bona fide researchers upon reasonable request and after signing a data sharing agreement ensuring that the data privacy of all participants is protected and all data are stored securely.

Textbox 1. Explanation of self-reported sleep quality score.

Score and description
• 5: Very refreshing
• 4: Rather refreshing
• 3: Moderately refreshing
• 2: Hardly refreshing
• 1: Not refreshing

Table 1. Collected data.

Source and name	Definition	Day or night
Wearable sensor: Everion (Biofourmis AG)		
HR	Heart rate	Day and night
SDNN	SD of IBIs[a]	Day and night
SD1	SD of distance from 45° line of Poincaré plot of consecutive IBIs	Day and night
SD2	SD of distance from –45° line of Poincaré plot of consecutive IBIs	Day and night
Step count	Step count based on arm motion	Day and night
Sleep duration	Estimated based on acceleration and HR data	Night
Awake duration	Estimated based on acceleration and HR data	Night
Visual crossing [40] API[b] service		
Temperature	Extracted via API using location recorded through smartphone app	Day
Prestudy questionnaires and medical assessments		
EDSS [41]	Expanded Disability Status Scale	—[c]
MSSS [42]	Multiple Sclerosis Severity Score	—
ARMSS [43]	Age Related Multiple Sclerosis Severity Score	—
ANS[d] dysfunction	Assessed using COMPASS[e] [44] questionnaire	—
MS[f] diagnosis	Patient with MS or control group	—
MS type	None, progressive MS disease state, or relapse remitting MS disease state	—
Custom smartphone app		
Sleep quality	Scale from 1 to 5 as outlined in Textbox 1	Night
Stress	Self-reported multiple times a day a scale from 1 to 10	Day
Awake at night	—	Night
Sleep medication	—	Night

[a]IBI: interbeat interval.

[b]API: application programming interface.

[c]Not applicable.

[d]ANS: autonomic nervous system.

[e]COMPASS: Computerized Pilot Aptitude Screening System.

[f]MS: multiple sclerosis.

Data

A summary of all collected data can be found in Table 1.

We collected data mainly from 3 different sources: a wearable sensor, a custom smartphone app, and prestudy questionnaires or medical assessments. Nonstatic data were aggregated every day separately for when the participants were awake and asleep. For nonstatic variables, we calculated the minimum, mean, maximum, ratio of minimum to mean, and ratio of maximum to mean. For the static variables Expanded Disability Status Scale (EDSS), MS Severity Score (MSSS), Age-Related Multiple Sclerosis Severity Score (ARMSS), and ANS dysfunction, we used 3, 3, 4, and 17 as cutoff points, respectively, to transform them into binary variables. For the control group, we set these values to 0 before applying the cutoff rule. The custom smartphone app was distributed through the Google Play Store in Switzerland. Participants who did not own an Android phone were equipped with the Google Pixel 3 for the duration of the study.

Data Processing

For the analysis of HR and HRV, we only included periods where participants were resting as recommended for photoplethysmography-based HRV measurements [45]. Participants were classified as resting during 5-minute windows if their HR (measured in bpm) was <0.55 × (220 bpm – age) [46].

Furthermore, we transformed HRV recordings to normative values considering age, sex, and time of day [47]. The recorded data per participant was split into daily intervals based on when the participants woke up and aggregated as outlined in Table 1.

The times when participants went to bed and woke up were estimated manually based on HR, acceleration data from the

wearable sensor, and step count. To remove periods where the participants were in a transitional state between awake and asleep, we excluded 1 hour of data before and after the estimated going-to-bed and wake-up times.

All analysis was done in Python (version 3.8, Python Software Foundation). For modeling, we made use of the scikit-learn, keras, and XGBoost libraries [48-50].

Results

Overview

In this study, we analyzed the drivers of perceived sleep quality via predictive modeling. We first looked at significant differences in average perceived sleep quality between different subgroups of the participants. Subsequently, we compared the performance of different models for perceived sleep quality normalized per participant. Finally, we analyzed the variables where relative changes are calculated to significantly affect participants' sleep quality compared to their personal average over the 2 weeks.

For the analysis, data were available on average for 19.7 hours per day per participant (ie, approximately 82% of the time, SD 2.64 hours). This was consistent across patients with MS and healthy controls. Besides nonwear, reasons for data not being available at all times include participants switching between the 2 devices they had been equipped with for charging and subsequent synchronization issues.

Differences in Sleep Quality Across Subgroups

The average self-reported sleep score was 3.72 (scale from 1 to 5; Textbox 1). The distribution of responses is shown in Multimedia Appendix 3. Table 2 lists the observed mean differences and significances according to Wilcoxon rank sum tests for subgroups defined by sex, patient status, type of MS, dysfunction of the ANS, affection of the spinal cord, and severity of MS in terms of scores on the EDSS [41] and variations thereof (MSSS [42] and ARMSS [43]) measuring MS-related disability. We chose Wilcoxon signed rank tests (aka Mann-Whitney *U* test) over alternative methods, such as *t* tests, because they are rank based and distribution-free. Therefore, they are a natural choice for ordinal data (such as items on a Likert scale) as well as nonnormally distributed or binary data.

Table 2 shows the outcome of distribution-free 2-sided Wilcoxon signed rank tests for mean shifts in self-reported sleep quality between subgroups defined based on demographic information, patient status, and disease state. A higher reported sleep quality score corresponds to higher perceived sleep quality (Textbox 1). *P* values are calculated based on distribution-free 2-sided Wilcoxon signed rank tests for mean shifts in self-reported sleep quality between two groups of participants.

The perceived sleep quality score of female participants was significantly lower, indicating that their perceived sleep quality was higher than that for male participants. Participants with different types of MS did not report sleeping significantly differently. However, participants whose spinal cord was affected by lesions or with ANS dysfunction reported significantly lower perceived sleep quality—similar to participants scoring high on the MSSS, ARMSS, and EDSS scales. Apart from ANS dysfunction, the differences were not (as) significant when including the control group. However, for patients with MS, the severity of MS led to significant differences in perceived sleep quality.

Table 2. Mean comparison of the self-reported sleep quality score between different subgroups.

Group 1		Group 2		*P* value
Description, n (%)	Sleep quality score, mean (SD)	Description, n (%)	Sleep quality score, mean (SD)	
Sex				
Female, 48 (62)	3.84 (0.60)	Male, 29 (38)	3.54 (0.62)	.01
Disease status				
No MS[a], 24 (31)	3.71 (0.48)	Patients with MS, 53 (69)	3.73 (0.68)	.56
No MS, 24 (31)	3.71 (0.48)	MS type PMS[b], 9 (12)	3.64 (0.57)	.73
No MS, 24 (31)	3.71 (0.48)	MS type RRMS[c], 44 (57)	3.75 (0.70)	.43
MS type PMS, 9 (12)	3.64 (0.57)	MS type RRMS[c], 44 (57)	3.75 (0.70)	.64
ANS[d] dysfunction				
No dysfunction of ANS: all[e], 53 (69)	3.86 (0.52)	Dysfunction of ANS[f], 24 (31)	3.42 (0.73)	<.001
No dysfunction of ANS: MS[e], 29 (38)	3.99 (0.52)	Dysfunction of ANS[f], 24 (31)	3.42 (0.73)	<.001
Spinal cord status				
Spinal cord unaffected: all[e], 53 (69)	3.82 (0.53)	Spinal cord affected[f], 24 (31)	3.51 (0.77)	.10
Spinal cord unaffected: MS[e], 29 (38)	3.91 (0.55)	Spinal cord affected[f], 24 (31)	3.51 (0.77)	.06
MS-related disability				
MSSS[g]<3: all[e], 54 (70)	3.80 (0.58)	MSSS≥3[f], 23 (30)	3.55 (0.69)	.14
MSSS[g]<3: MS[e], 30 (39)	3.87 (0.64)	MSSS≥3[f], 23 (30)	3.55 (0.69)	.07
ARMSS[h]<5: all[e], 42 (55)	3.84 (0.53)	ARMSS≥6[f], 6 (8)	3.59 (0.70)	.17
ARMSS[h]<5: MS[e], 18 (23)	4.00 (0.55)	ARMSS≥6[f], 6 (8)	3.59 (0.70)	.05
EDSS[i]<3: all[e], 59 (77)	3.77 (0.56)	EDSS≥3[f], 18 (23)	3.58 (0.79)	.09
EDSS[i]<3: MS[e], 35 (45)	3.81 (0.61)	EDSS≥3[f], 18 (23)	3.58 (0.79)	.04

[a]MS: multiple sclerosis.

[b]MS type PMS: progressive MS disease state.

[c]MS type RRMS: relapse remitting MS disease state.

[d]ANS: autonomic nervous system.

[e]A group called “condition: all” refers to all participants for whom the condition is true (patients with MS as well as control group). A group called “condition: MS” refers only to participants diagnosed with MS for whom the condition is true (ie, no control group).

[f]All participants for whom this condition is true were diagnosed with MS.

[g]MSSS: Multiple Sclerosis Severity Score [42]. Per definition of the MSSS, the chosen cutoff point distinguishes between light to no disability (≤3) and more severe implications (>3).

[h]ARMSS: age-related multiple sclerosis severity score [43]. Per definition of the ARMSS, the chosen cutoff point distinguishes between light to no disability (≤4) and more severe implications (>4).

[i]EDSS: Extensive Disability Status Scale [41]. Per definition of the EDSS, the chosen cutoff point distinguishes between light to no disability (≤3) and more severe implications (>3).

Comparison of Different Modeling Techniques for Normalized Perceived Sleep Quality

Higher-dimensional “black box” methods have outperformed clearly explainable and interpretable techniques such as GLMs and thus have gained more and more popularity for medical applications. For binary classification, neural networks [33] and tree ensemble methods [51] tend to outperform logistic regression in recent literature. However, logistic regression naturally models the changes in odds for a binary outcome, allowing for very easy and clear interpretation. The following is a comparison of these modeling techniques as well as a generalized additive model (GAM) and support vector machine applied to model perceived sleep quality as part of our study.

To analyze how relative changes in input features affect perceived sleep quality compared to participants’ average responses, we normalized input features and the perceived sleep quality response. We subtracted the mean value per participant across the 2 weeks and divided by the respective SD for each

participant. As the normalized sleep quality response failed the Shapiro-Wilk normality test (P<.001), thus violating one of the assumptions of linear regression, we transformed the problem into the binary setting. We split the data into high-quality and low-quality sleep based on whether a participant slept better than their personal average recorded during the study. The performances of the different models listed in Table 3 are similar (63%-67% accuracy). For all models, we used 0.5 as a cutoff point to classify between high- and low-quality sleep. The best performing model is the GAM, achieving an accuracy of 67% with an area under the curve (AUC) of 0.71. The support vector machine, logistic regression (GLM), and symmetric boosted trees achieve the same accuracy (65%). Of the 3, the support vector machine achieves the highest AUC with 0.70. Adding interaction terms to the logistic regression models (GLM of order 2 and 3) does not improve accuracy but only decreases AUC (from 0.69 to 0.66). In terms of accuracy, the neural network performs the worst out of the selected models with 63%. In terms of AUC, however, neural networks outperform boosted tree ensemble methods and GLMs with interaction terms.

While boosted trees and neural networks perform feature selection themselves, we constructed a sequential feature selection procedure for GLMs, the GAM, and the support vector machine.

Table 3. Model performances for predicting normalized perceived sleep quality using all available information recorded while participants were awake and asleep.

Model[a] comparison	Accuracy[b] (%)	Precision[b] (%)	Recall[b] (%)	AUC[c]
Support vector machine	65	66	64	0.70
Symmetrical boosted trees[d]	65	67	65	0.66
Neural network[e]	63	63	63	0.68
GLM[f]	65	66	65	0.69
GLM order 2[g]	65	65	65	0.68
GLM order 3[h]	65	65	65	0.66
Generalized additive model	67	67	67	0.71

[a]The models were evaluated on 50 perfectly balanced test sets, each consisting of randomly selected 20% of participants who were removed from the training set.

[b]Using a cutoff point of 0.5 for the calculated probabilities.

[c]AUC: area under the curve.

[d]Architecture chosen based on Bayesian optimization [52]: depth of 5 and 600 boosting rounds.

[e]Architecture chosen based on Bayesian optimization [52]: 2 hidden layers containing 16 neurons with hyperbolic tangent activation functions and dropout rates of 0.7 and 0.5, respectively.

[f]GLM: generalized linear model.

[g]In addition to the untransformed features, this model includes interactions between 2 variables.

[h]In addition to the untransformed features, this model includes interactions between up to 3 variables.

Modeling Normalized Perceived Sleep Quality

In this subsection, we analyze logistic regression models for normalized perceived sleep quality without interaction terms. Although GAMs outperformed GLMs, they fit effects as smoothing splines, making model comparison harder than in the generalized linear setting where effects on the modeled OR are assumed to be linear. Per participant, perceived sleep quality and input features were normalized by subtracting the average per participant and dividing by the respective SD per participant. We constructed 3 models with different input features to compare the consistency of effects depending on what information is available to the model. The first model (M1.1: night and day) uses all available data recorded during the night and the previous day to model normalized perceived sleep quality. The second model only uses data recorded, while the participants were asleep (M1.2: night), such as HR while asleep. The third model (M1.3: day) exclusively uses information recorded when the participants were awake, such as HR while awake. All 3 models include an L1 penalty to shrink the coefficient values of features without great explanatory power to 0. Table 4 lists variables that are statistically significant in at least 1 of the 3 models. As outlined in the previous section, logistic regression achieved an accuracy of 65% on a perfectly balanced test set when including features collected while participants were awake and asleep (M1.1).

Across M1.1 to M1.3 in Table 4, observed effects have a constant sign across all models that they are included in, indicating general consistency of calculated effects independent of included input features. In addition to whether a participant woke up during the night, the levels of stress they were exposed to the previous day, the duration of their sleep, and recorded motion while asleep, 8 HR- or HRV-related features significantly affected perceived sleep quality in 1 of the 3 models M1.1-M1.3. In M1.1-M1.3, increased sleep duration and decreased motion while asleep are calculated to affect sleep quality positively—so are increases in HRV while asleep in terms of average SD1, maximum SD2, and maximum SDNN and increases in minimal HR while asleep. In contrast, increases in average SD2 while asleep as well as increases in the ratio of

maximum SDNN while asleep to average SDNN while asleep are calculated to affect perceived sleep quality negatively. We found higher levels of stress throughout the previous day and if a participant woke up during the night to affect perceived sleep quality negatively.

Table 4 shows variables that are statistically significant ($P<.10$) in at least 1 logistic regression model for normalized self-reported sleep quality without interaction terms where feature selection was performed for both groups simultaneously but the models were calculated for participants with MS and the control group separately. Positive values increase the chances of better self-reported sleep quality according to the fitted logistic regression model.

Table 4. Statistically significant variables for normalized perceived sleep quality for patients with multiple sclerosis and the control group.

	M1.1: night and day as input, model coefficient (*P* value)	M1.2: night as input only, model coefficient (*P* value)	M1.3: day as input only, model coefficient (*P* value)
Mean stress awake	—[a]	—	–0.14 (.04)
HR[b] minimum ratio awake	0.16 (.03)	—	—
Sleep duration	0.47 (<.001)	0.46 (<.001)	—
Awake at night	–0.58 (<.001)	–0.58 (<.001)	—
Motion asleep	–0.29 (.02)	–0.29 (.02)	—
Minimum HR asleep	—	0.13 (.04)	—
Mean SD1[c] asleep	0.30 (.004)	0.26 (.01)	—
Minimum SD2[d] asleep	—	–0.18 (.06)	—
Mean SD2 asleep	–0.47 (.01)	–0.43 (.02)	—
Maximum SD2 asleep	0.08 (.03)	0.06 (.04)	—
Maximum SDNN[e] asleep	0.51 (<.001)	0.47 (<.001)	—
SDNN maximum ratio asleep	–0.54 (.01)	–0.52 (.01)	—

[a]—: The variable was not included in that respective model (ie, removed during iterative feature selection process).

[b]HR: heart rate.

[c]SD1: SD of distance from the 45° line of the Poincaré plot of consecutive interbeat intervals.

[d]SD2: SD of distance from the –45° line of the Poincaré plot of consecutive interbeat intervals.

[e]SDNN: SD of interbeat intervals.

Differences Between Patients With MS and the Control Group

We analyze differences in effects between the control group and participants with MS by computing the 3 logistic regression models M1.1-M1.3 for normalized perceived sleep quality separately for the 2 groups (Table 5). We refer to these models as M2.1-M2.3. They are based on the feature selection performed for M1.1-M1.3, but the statistical significance of effects are calculated for the 2 groups separately, thus analyzing the stability of the calculated effects across the 2 groups. The performance of M2.1 dropped from an accuracy of 65% for M1.1 to 60% accuracy for the control group and 64% for participants with MS. Furthermore, we constructed 3 more logistic regression models, M3.1-M3.3, where the included features are optimized for the control group and the patient group separately (Table 6). Figure 1 visually summarizes Table 6. For the models M2.1-M2.3, the calculated effects for the same variables have the same sign in all cases apart from 2, indicating largely agreeing effects across the subgroups. When optimizing the feature selection for each subgroup, we observe divergence in the included features and an improvement in performance (accuracy increases to 68% for the control group and remains at 64% for participants with MS).

The effect of increases in minimal HR while asleep is calculated to be positive and statistically significant at α=1% in M2.1 and M2.2 for participants with MS but not statistically significant and negative for the control group. The effect of increases in reported stress levels in M2.3 is statistically significant ($P<.01$) for patients with MS and the control group, yet <0.005 in absolute terms for the control group.

In M3.1 and M3.2, sleep duration and being awake at night are selected for both subgroups. For both effects, sign, statistical significance, and general magnitude were the same. We find stress, motion while asleep, minimal HR while asleep, and maximum SD1 while asleep to only significantly affect perceived sleep quality for participants with MS. In contrast, the amount of time spent awake before going to bed and minimal SD1 while awake only affected perceived sleep quality for participants of the control group.

Table 5. Differences in statistically significant variables for perceived sleep quality between patients with multiple sclerosis and the control group: simultaneous feature selection.

	2.1: Night and day as input, model coefficient (*P* value)		2.2: Night as input only, model coefficient (*P* value)		M2.3: day as input only, model coefficient (*P* value)	
	Patients with multiple sclerosis	Control group	Patients with multiple sclerosis	Control group	Patients with multiple sclerosis	Control group
Mean stress awake	—[a]	—	—	—	–0.19 (.01)	–0.00 (.001)
HR[b] minimum ratio awake	0.20 (.01)	0.13 (.39)	—	—	—	—
Sleep duration	0.37 (<.001)	1.21 (.002)	0.40 (<.001)	0.72 (<.001)	—	—
Awake at night	–0.56 (.001)	–1.01 (.06)	–0.57 (.001)	–0.66 (.07)	—	—
Motion asleep	–0.28 (.03)	–0.40 (.21)	–0.29 (.02)	–0.24 (.23)	—	—
Minimum HR asleep	—	—	0.25 (.004)	–0.21 (.19)	—	—
Mean SD1[c] asleep	0.28 (.01)	0.47 (.10)	0.21 (.08)	0.40 (.004)	—	—
Minimum SD2[d] asleep	—	—	–0.27 (.02)	–0.09 (.27)	—	—
Mean SD2 asleep	–0.32 (.06)	–1.37 (.09)	–0.47 (.02)	–0.24 (.19)	—	—
Maximum SD2 asleep	0.08 (.04)	0.25 (.21)	−0.31 (.32)	0.08 (.03)	—	—
Maximum SDNN[e] asleep	0.39 (.001)	1.25 (.07)	0.99 (.06)	0.17 (.007)	—	—
SDNN maximum ratio asleep	–0.47 (.03)	–1.41 (.10)	–0.67 (.01)	–0.17 (.22)	—	—

[a]—: The variable was not included in that respective model (ie, removed during iterative feature selection process).

[b]HR: heart rate.

[c]SD1: SD of distance from the 45° line of the Poincaré plot of consecutive interbeat intervals.

[d]SD2: SD of distance from the –45° line of the Poincaré plot of consecutive interbeat intervals.

[e]SDNN: SD of interbeat intervals.

Table 6. Differences in statistically significant variables for perceived sleep quality between patients with multiple sclerosis and the control group: separate feature selection.

	M3.1: night and day, model coefficient (*P* value)		M3.2: night, model coefficient (*P* value)		M3.3: day, model coefficient (*P* value)	
	Patients with multiple sclerosis	Control group	Patients with multiple sclerosis	Control group	Patients with multiple sclerosis	Control group
Mean stress awake	—[a]	—	—	—	–0.19 (.02)	—
Awake duration	—	0.43 (.05)	—	—	—	—
Minimum SD1[b] awake	—	—	—	—	—	0.48 (.05)
Sleep duration	0.39 (<.001)	0.93 (<.001)	0.42 (<.001)	0.82 (<.001)	—	—
Awake at night	–0.53 (.001)	—	–0.56 (.002)	–0.86 (.06)	—	—
Motion asleep	–0.26 (.02)	—	–0.28 (.02)	—	—	—
Minimum HR[c] asleep	0.08 (<.001)	—	0.27 (.002)	—	—	—
Maximum SD1 asleep	0.17 (.02)	—	0.18 (.04)	—	—	—

[a]—: The variable was not included in that respective model (ie, removed during iterative feature selection process).

[b]SD1: SD of distance from 45° line of Poincaré plot of consecutive interbeat intervals.

[c]HR: heart rate.

Figure 1. Approximate visualization of the statistically significant effects of M3.1-M3.3 for patients with multiple sclerosis (MS; upper half) and the control group (lower half), as displayed in Table 6. In this visualization, only the order of the effects for each of the 2 groups separately is correct. The distances are not proportional to the calculated effects (Table 6). Sleep continuity refers to "awake at night" in Tables 4-6, that is, whether participants woke up at night normalized across the duration of the study. HR: heart rate; max: maximum; min: minimum; SD1: SD of distance from 45° line of Poincaré plot of consecutive interbeat intervals.

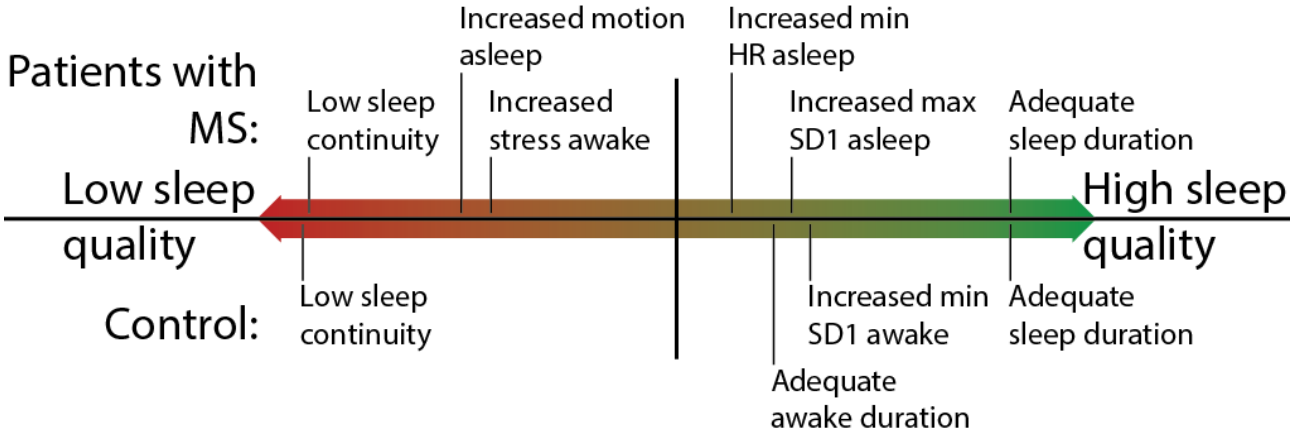

Table 5 shows variables that are statistically significant (P<.10) in at least 1 logistic regression model for normalized self-reported sleep quality without interaction terms where feature selection was performed for both groups simultaneously, but the models were calculated for participants with MS and the control group separately. Positive values increase the chances of better self-reported sleep quality according to the fitted logistic regression model.

Table 6 shows variables that are statistically significant (P<.10) in at least 1 logistic regression model for normalized self-reported sleep quality without interaction terms where feature selection was performed for participants with MS and the control group separately. Positive values increase the chances of better self-reported sleep quality according to the fitted logistic regression model.

Correlating Input Factors of the Logistic Regression Models

Multiple input factors of the different models for normalized perceived sleep quality (M3.1-M.3.3) correlated statistically significantly (Multimedia Appendix 3). To highlight shared information content between multiple models, Multimedia Appendix 4 displays Pearson correlations for features selected for M3.1-M3.3, where the feature selection and computation of the statistical significance of effects were performed separately for participants with MS and the control group. The correlations are calculated separately for participants with MS and the control group, allowing for comparison of the relation between the 2 groups. In total, 2 pairs of input variables for M3.1-M3.3 correlated particularly strongly with a correlation coefficient of –0.41 to –0.49 (P<.001): the pair of duration of sleep and the duration participants spent awake before going to bed and the pair of average SD1 while asleep and minimal HR while asleep. Interestingly, there are also 3 pairs where the difference in correlation between the control group and the participants with MS was particularly high. First, minimal HR while asleep and motion while asleep correlated with a coefficient of .11 for participants with MS but with a coefficient of –0.09 for the control group. Second, minimal HR while asleep and recorded stress levels correlated with a correlation coefficient of –0.17 for participants with MS but with a coefficient 0.06 for the control group, indicating a difference in response to stress. Third, the duration participants spent awake before going to bed and the recorded levels of stress correlated with a coefficient of –0.12 for participants with MS but 0.09 for the control group, further indicating a potential difference in behavior as a reaction to stress.

Discussion

Principal Findings

In this study, we analyzed how the ANS, the cardiovascular system, stress, activity, and demographic information affect perceived sleep quality for patients with MS and a control group. Model performances suggest that relative changes in perceived sleep quality per participant can indeed predict perceived sleep quality using a combination of HRV metrics, activity data, and stress (M1.1-M3.3). Generally, we find greater HRV to significantly improve perceived sleep quality. However, we find that activation of stress response (high sympathetic and low parasympathetic activity), similar to higher levels of perceived stress, significantly decreases perceived sleep quality. For the control group, this effect is less severe.

With stress levels and sleep duration, we find predictors particularly important for the sleep quality of patients with MS that can be at least partially acted upon to improve perceived sleep quality. However, calculated effects regarding signals that are not directly controllable (eg, HRV) are much more difficult to translate into actionable recommendations. For the effects of HR and HRV, further studies are needed to better understand the underlying drivers of these signals and how they can be acted upon.

Effects of HRV on Sleep Quality

We found various HRV metrics to be suitable predictors for perceived sleep quality. In particular, increased SD1 metrics positively impacted normalized perceived sleep quality across M1.1-M3.3, highlighting their consistency for patients with MS as well as the control group. However, the calculated effects of SD2 and SDNN seemed contradictory and inconsistent in

M1.1-M1.3 and were not selected when the automated feature selection procedure was conducted separately for participants with MS and the control group for M3.1-M3.3.

There are various factors that influence ANS activity and thus also HRV metrics. While participants are awake, physical activity, stress, overall mood, and deep breathing [53,54] might impact HRV metrics. In the long run, ANS activity is also affected by MS disease progression [16].

While asleep, a possible explanation for the calculated effects of increased activity of the sympathetic and parasympathetic nervous system is their behavior during rapid eye movement (REM) and non-REM sleep phases and their connection to stress. HRV fluctuates strongly between different phases of sleep [25,55-57] and is particularly high during REM sleep. More time spent in REM sleep phases was found to increase subjective sleep quality and also cognitive performance [58], which matches the calculated effects regarding the sympathetic and parasympathetic nervous system. While the activity of the former increases during REM sleep compared to non-REM sleep, the activity of the latter decreases during REM sleep phases [59]. Furthermore, the sympathetic nervous system regulates the fight-or-flight response and gives an indication of stress levels. The negative effect of increases in sympathetic activity and positive effect of increased parasympathetic activity on sleep quality might thus indicate that participants experienced stress throughout the day, which carried on into their sleep (activated stress response), or that participants went through stressful experiences during their REM sleep, which might again be impacted by experienced stress while awake. As outlined in M1.3-M3.3, we found increased stress to reduce perceived sleep quality, thus matching the effects outlined above.

Effects of MS Diseases Status on Sleep Quality

Symptoms of severe MS significantly decreased perceived sleep quality. However, we did not find significant differences in subjective sleep quality between participants diagnosed with MS and the control group. This indicates that MS itself does not affect perceived sleep quality. However, scoring high on the ARMSS, MSSS, or EDSS scale and affection of the spinal cord or ANS resulted in significantly worse sleep for patients with MS. Thus, symptoms that were found to decrease general quality of life for patients with MS also contribute to lower perceived sleep quality, matching previous studies [3,16,30,60].

Effects of Sleep Duration and Awake Duration on Sleep Quality

We generally found increased sleep duration to positively affect perceived sleep quality. The effects were statistically significant for participants with MS as well as the control group across M1.1-M3.3 and are rather unsurprising. This is a further indication of the importance of an adequate sleep schedule to achieve high-quality sleep and increase quality of life. For patients with MS as well as healthy individuals, this offers an opportunity to improve their sleep quality and subsequently quality of life. Furthermore, at least for the control group, longer times spent awake before going to bed positively affected their perceived quality of sleep. This seems in contrast to the positive effect of longer sleep duration; however, this might indicate that too little time spent awake negatively impacts perceived sleep quality. The 2 effects of longer sleep duration and longer awake duration thus highlight the need of a balance between the time spent awake and asleep.

Effects of Stress on Sleep Quality

We found stress levels (self-reported) to have a statistically significant negative impact on perceived sleep quality. For participants with MS, stress impacted perceived sleep quality more strongly than it did for the control group (Table 6). Furthermore, for participants with MS, stress correlated significantly negatively with awake duration and minimal HR while asleep. This indicates that stress more severely affects patients with MS, which is even measurable using their minimal HR while asleep. The significant negative correlation of stress to awake duration for participants with MS, which is positive but statistically insignificant for the control group, might indicate that stress even impacted the daily routine of participants with MS.

These effects are consistent with existing literature [26-28,61]. For patients with MS, several studies suggest that increased stress increases the chances of relapse [62] and influences inflammatory activity [63]. Furthermore, the ANS is a stress response system. The more severe effect of stress on sleep quality for participants with MS might thus be another symptom of a dysfunctional ANS.

While we do not find reported stress levels to impact the sleep quality for the control group, we observe negative effects of increases in sympathetic activity (SDNN and SD2) in M2.1-M2.3 for patients with MS as well as the control group. The sympathetic nervous system controls the fight-or-flight response, and stress might cause an activated stress response, which is characterized by increased sympathetic activity and decreased parasympathetic activity. This indicates a negative effect of stress on perceived sleep quality for both groups, although not observable through reported stress levels for the control group.

While we calculate similar effects for perceived stress and objective measures of stress (ie, an activated stress response), perceived stress ratings and objective assessments of stress do not have to align [64]. Comparisons between objective and subjective assessments of stress must thus be treated carefully.

Effects of Motion (Steps) on Sleep Quality

An increase in recorded arm motion between initially falling asleep and waking up in the morning significantly decreased perceived sleep quality. The recorded motion records both steps of participants (eg, to use the bathroom) and general movement while asleep due to low sleep continuity or a sleep disorder, such as period leg movement disorder. Period leg movement disorder affects 8% to 11% of the population [65] and around 25% of patients with MS [13,18,66]. Generally, excessive motion indicates disruption of sleep. Recorded motion during the night furthermore correlates significantly with being awake at night (r=0.22; P=.004). The negatively calculated effects for increases in both variables match existing literature about sleep continuity [67] as well as compartment 5 of the Pittsburgh Sleep Quality Index [24].

Effects of HR on Sleep Quality

Despite various HR-based variables being included in M1.1-M2.3, only minimal HR while asleep significantly affected perceived sleep quality for patients with MS in M3.1-M3.2. While the effect of increases in minimal HR seems consistent for patients with MS, it seems to have no effect on sleep quality for the control group. This highlights a difference in the effect of cardiovascular activity between the 2 groups.

Effects of Weather (Temperatures) on Sleep Quality

We did not find temperature to affect perceived sleep quality in our study, contradicting previous research about the influence of weather on sleep quality [68] and temperatures on the well-being of patients with MS [69]. However, past research suggests that mainly the room temperature when falling asleep impacts sleep [70]. The overall temperature outside, as recorded during our study, is only a (poor) estimate of room temperature.

Relation Between Demographic Information and Sleep Quality

Female participants slept significantly better (subjectively) compared to male participants in our study. This is contradicting existing literature on objective sleep quality where female participants were found to sleep significantly worse and also shorter than male participants [71,72]. Furthermore, women were also found to be 1.41 times more likely to experience insomnia compared to men [73].

Matching previous studies [71,74], we found age to correlate strongly with motion while asleep and being awake at night (Pearson correlation of r=0.31 and r=0.23, respectively, with P<.001). Both factors are calculated to significantly reduce sleep quality (M1.1-M3.2), which matches existing literature about reduced sleep continuity of older individuals [74].

Limitations

Our study has several limitations that question the generalizability and immediate clinical applicability of our results.

First, because we collect ANS activity passively, we cannot control all the factors that influence ANS activity and might confound our results. In the long run, ANS activity is influenced by disease progression for patients with MS [16]. Temporarily, ANS activity might be influenced by deep breathing exercises, shock, mood, physical exercise, and generally any type of stressor [53,54]. As we aggregate ANS activity over multiple hours when participants are either awake or asleep, it seems unlikely that we capture either very short bursts of ANS activity or long-term trends caused for instance by MS disease progression. The multitude of factors that influence ANS activity, however, only allow for hypothesis about the exact causes of the effects we observe. This uncertainty makes the translation into actionable clinical recommendations difficult.

Second, the translation of our findings into clinical recommendations is further limited because many effects found to be important for sleep quality estimation are based on signals collected while participants are asleep. Our analysis does not reveal what actions cause variables such as minimal HR while asleep to differ. Thus, we can only provide recommendations for variables such as stress or sleep duration.

Third, despite the diversity within our study population, it is unlikely that it covers the diverse range of MS disease traits. As we recruited patients with MS solely at the neuroimmunology department of the University Hospital Zurich, our study is effectively limited to Switzerland. While our findings regarding ANS activity might generally be assumed to generalize to patients with MS outside of Switzerland, there are likely several confounders that bias our findings due to specifics of the life in Switzerland, its health care sector, or the genetic traits of Switzerland's population. As part of a larger and more representative study, it would also be possible to stratify for disease progression and ANS dysfunction to investigate the robustness of our findings toward particularly severe cases of MS with a highly dysfunctional ANS.

Finally, we investigate self-reported sleep quality, which does not have to align well with objective measures of sleep quality [75]. While we find objective measures of sleep quality to be strong predictors of perceived sleep quality and also normalize perceived sleep quality ratings per participant to remove intrasubject variability, our results have to be treated with care. Similarly, we investigate perceived stress ratings, which do not form a passive and objective measure of stress. Again, we find similar effects of objective measures of stress (ie, an activated stress response at night) and self-reported stress levels and also normalized stress ratings per participant. However, self-reported stress levels do not have to be consistent, and a comparison between self-reported and objectively assessed stress levels is difficult [64].

Generally, all the points above outline that a larger study is needed to confirm our findings and hopefully derive actionable insides. This will hopefully allow to derive what actions cause the observed changes in signals that are outside participants' direct control. We hope our study lays the basis for such larger efforts.

Future Research

In addition to addressing what is outlined in the Limitations section, there are multiple avenues worth exploring for future research.

First, we believe a better understanding of the ANS of each patient with MS would prove most valuable. This might be achieved via imaging, particularly through connectomes that provide a mapping of the nervous system's connectivity. Given recent successes in connectome-based predictive modeling [76], the mapping of connectomes of patients with MS to perceived sleep quality might prove an interesting first step. Similarly, an analysis of the location of lesions in the CNS might help to explain why the ANS of patients with MS might relate differently to perceived sleep quality. Subsequently, this might help to identify different subgroups of patients with MS, who might have to be treated differently to improve their sleep quality and quality of life.

Second, we believe incorporating information about sleep stages into the analysis might prove most valuable. As outlined in the Effects of HRV on Sleep Quality section, ANS activity

fluctuates between different sleep stages. Therefore, through or simple aggregation across the whole night, important patterns might currently be neglected.

Combined with large representative studies that are also able to establish causal relationships between participants' behavior and changes in bio signals, we believe this would paint a precise and representative picture of the connection between ANS activity of sleep quality more generally for patients with MS and heathy individuals alike.

Third, we believe a longitudinal study that captures potential disease progression in patients with MS would provide valuable insights into how sleep quality and ANS activity might change based on different stages of MS, including relapses. It would be most interesting to include interventions in such a study design to verify the causality of our results, for example, intervening on participants sleep duration.

Fourth, low sleep quality is a symptom of various neurological conditions such as Parkinson, epilepsy, or Huntington. Some of the results we derived might translate and prove valuable also to patients with other neurological conditions.

Conclusions

The results we present are 3-fold. First, we have found new predictors for the perceived sleep quality of patients with MS as well as healthy individuals, which are conveniently measurable using wearable sensors. We thereby gained a better understanding of the impact of HRV on sleep quality and the differences in effect for patients with MS, namely, an activated stress response (lower parasympathetic activity and higher sympathetic activity) while asleep impacts perceived sleep quality negatively. However, the activity of the parasympathetic nervous system has greater impact on perceived sleep quality than sympathetic activity, especially for healthy individuals.

Second, we found the disease state of patients with MS to impact perceived sleep quality. In particular, patients with MS whose ANS was dysfunctional; whose spinal cord was affected; or who scored highly on the MSSS, ARMSS, or EDSS reported significantly lower sleep quality than patients with MS whose ANS was not dysfunctional; whose spinal cord was unaffected; and who scored lower on the MSSS, ARMSS, or EDSS, respectively.

Third, for binary classification problems using medical sensor data, we provide further evidence for the use of more conventional models that are interpretable as well as explainable over state-of-the-art black box models. While GAMs outperformed all other models, GLMs performed similar to boosted tree ensemble classifiers or support vector machines and outperformed neural networks.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request. Accompanying code is available through the GitHub repository [77].

Authors' Contributions

MH, LB and the entire Personalized Health and Related Technologies consortium initialized the study. PO and LB built the study apparatus; PO, LB and MH conducted the study. MM and CH prepared the collected data, conducted the data analysis, and wrote the main manuscript. All authors reviewed the paper and contributed to the discussion of calculated effect.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patients with multiple sclerosis on disease-modifying therapy.
[DOCX File , 14 KB - neuro_v3i1e48148_app1.docx]

Multimedia Appendix 2
Patients with multiple sclerosis on medication that is known to affect heart rate variability.
[DOCX File , 14 KB - neuro_v3i1e48148_app2.docx]

Multimedia Appendix 3

Distribution of sleep quality ratings.
[PNG File , 11 KB - neuro_v3i1e48148_app3.png]

Multimedia Appendix 4
Correlation between input variables to models M3.1-M3.3.
[DOCX File , 18 KB - neuro_v3i1e48148_app4.docx]

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Abbreviations

ANS: autonomic nervous system
AUC: area under the curve
DMT: disease-modifying treatment
EDSS: Expanded Disability Status Scale
GAM: generalized additive model
GLM: generalized linear model
HR: heart rate
HRV: heart rate variability
IBI: interbeat interval
MS: multiple sclerosis
REM: rapid eye movement
SDNN: SD of interbeat intervals

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Original Paper

Virtual Reality–Based Neurorehabilitation Support Tool for People With Cognitive Impairments Resulting From an Acquired Brain Injury: Usability and Feasibility Study

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Abstract

Background: Acquired brain injury (ABI) is a prominent cause of disability globally, with virtual reality (VR) emerging as a promising aid in neurorehabilitation. Nonetheless, the diversity among VR interventions can result in inconsistent outcomes and pose challenges in determining efficacy. Recent reviews offer best practice recommendations for designing and implementing therapeutic VR interventions to evaluate the acceptance of fully immersive VR interventions.

Objective: This study aims to evaluate the usability and feasibility of a co-designed VR-based neurorehabilitation support tool by conducting multiple proof-of-concept trials in a sample of patients with ABI within a hospital setting.

Methods: A single session deploying custom immersive serious games to train cognitive functions using a new-generation head-mounted display was conducted among a sample of inpatients with ABI. Structured questionnaires were administered at the end of the session to evaluate the usability of the system and the intervention, participants' familiarity with the technology, and any adverse effects related to cybersickness. Additionally, the training duration while wearing the headset and the demographic characteristics of the participants were considered.

Results: A total of 20 patients with ABI participated in a 1-hour proof-of-concept trial. The mean usability score was 37 (SD 2.6) out of 40, the technology familiarity level was 9.2 (SD 2.9) out of 12, and the Simulator Sickness Questionnaire total score was 1.3 (SD 2). On average, participants wore the headset for approximately 25.6 (SD 4.7) minutes during the intervention. There were no substantial differences in usability and technology familiarity levels based on patients' etiology or age, with no notable symptoms of cybersickness reported. Significantly strong correlations were noted between cybersickness symptoms and various usability categories, including exposure, motivation, interactivity, task specificity, and immersion aspects. Further, there was a significant association between the intervention time and the number of tasks performed (P<.001). Furthermore, patients who derived enjoyment from VR sessions expressed a heightened interest in incorporating VR into their daily neurorehabilitation practice (P<.001). Moreover, oculomotor issues were found to be highly sensitive to the onset of disorientation sickness symptoms (P<.001).

Conclusions: Through a collaborative approach, this study showcases the usability and feasibility of a VR-based support tool for cognitive rehabilitation among inpatients with ABI. Key components of such interventions encompass a multidisciplinary array of immersive experiences integrating neurorehabilitation principles and serious games techniques.

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KEYWORDS

acquired brain injury; virtual reality; head-mounted display; neurorehabilitation; usability; feasibility; co-design; multidisciplinary experiences; immersive serious games

Introduction

Background

Acquired brain injury (ABI) is any postnatal brain damage that is not hereditary, congenital, or degenerative [1], and encapsulates 2 main categories, namely, traumatic brain injury (TBI) and non-TBI [2]. TBI is an external traumatic event in which injury to the brain is sustained. It is the most frequent etiology of ABI and is primarily caused by falls and road injuries. In 2016, there were 27.08 million new cases of TBI and 55.5 million prevalent cases worldwide [3]. The incidence of TBI is likely to continue rising, driven by factors such as population growth, aging demographics, and increased motor vehicle usage. By contrast, non-TBI arises from internal disease processes, such as brain tumors, causing damage to brain tissue. The primary cause of non-TBI is stroke, with ischemic stroke accounting for 62.4% of all new strokes globally, followed by hemorrhagic stroke at 37.6% [4]. In recent years, there has been a significant increase in stroke rates among young individuals, a trend expected to persist, especially in low-income countries. ABI not only results in health deterioration and disability for affected individuals and their families but also imposes a substantial burden on health care systems and economies due to lost productivity and high health care costs [2].

Individuals with ABI exhibit adverse outcomes across multiple functional domains, encompassing sensorimotor, cognitive, and behavioral areas, which impede the performance of basic activities of daily living [1]. Regarding cognitive function, deficits commonly manifest in attention, memory, and executive functions [4]. The majority of patients with TBI experience challenges with sustained, selective, or divided attention, along with diminished information processing speed. Memory issues often involve a heightened rate of forgetting, as well as slower, disorganized, and incoherent learning compared with individuals without TBI. Additionally, patients with TBI commonly exhibit executive function alterations, including difficulties in planning, limited mental flexibility, reduced inhibitory ability, and challenges in verbally recalling phonetic categories [5,6]. Cognitive impairment following a stroke varies based on factors such as the nature of the stroke, the specific brain regions affected, and the stage of recovery. Individuals may exhibit hemispatial neglect as well as various types of visuoperceptive and visuospatial impairments. Additionally, deficits in verbal memory and language-related issues are common, including aphasia, which can affect writing and reading abilities [6,7].

Although some impairments may show improvement over time, recovery rates vary as a result of differences in the baseline characteristics of individuals [6]. Furthermore, despite the distinct disease processes and medical issues associated with TBI and non-TBI, patients often receive treatment and rehabilitation in the same hospital facilities. To achieve optimal clinical outcomes for all patients with ABI, health care professionals need to deliver personalized and targeted treatments, necessitating a comprehensive understanding of the pathology across different categories of ABI [2].

Neurorehabilitation is a meticulously supervised process designed to assist individuals with ABIs in reclaiming their functional abilities and enhancing their quality of life. Fundamental components of neurorehabilitation encompass a spectrum of expert and multidisciplinary assessments, the implementation of realistic and goal-oriented tasks, and the evaluation of clinically appropriate outcome measures. Importantly, this evaluation also takes into account the perspectives of both the patient and their family [8]. Neurorehabilitation services serve as a bridge between isolation and exclusion, often representing the initial stride toward attaining fundamental rights. Health, indeed, is a fundamental right, and neurorehabilitation stands as a potent service that fosters personal empowerment, enhances independence, and notably facilitates the return to work and active participation within the community [1,8,9].

Virtual reality (VR) is emerging as a swiftly advancing technology, garnering recent popularity as a promising support tool for neurorehabilitation among individuals with ABI [10-13]. Using VR in rehabilitation represents a versatile, captivating, and multifaceted approach capable of addressing patients' sensorimotor and cognitive capacities, thereby eliciting positive responses. It enhances treatment compliance while augmenting levels of functioning and overall quality of life [14]. VR provides a platform to simulate real-life scenarios and ecologically valid activities within a safe and controlled environment [15].

As the term "virtual reality" can encompass various computer-based rehabilitation system types across studies and may influence the feasibility and efficacy of interventions, maintaining consistent terminology is crucial [12,16]. In 1999, Brooks [17] defined a VR experience as "any in which the user is effectively immersed in a responsive virtual world. This implies user dynamic control of viewpoint." Thus, for a system to be considered VR based, it must fulfill 3 conditions: it should be immersive, interactive, and true to reality.

Modern high-end VR systems can provide users with an immersive experience, wherein they feel surrounded by a computer-generated world that responds naturally and convincingly, while also minimizing side effects such as

cybersickness [18]. The utilization of new-generation head-mounted displays (HMDs) enables stereoscopic perception and perspective changes based on the user's viewpoint. Additionally, incorporating haptic controllers and precise tracking of 6 degrees of freedom allow the system to accurately recognize users' motion (both position and orientation) in 3-dimensional space. Furthermore, contemporary computing techniques and advanced rendering methods facilitate the development of highly detailed graphics and real-time responses [19]. Consequently, users can engage in a realistic virtual environment, interacting with intuitive gestures that mimic their real-world movements. This immersive experience often leads to a profound sense of presence and may even induce a phenomenon referred to as "virtual embodiment" [11,20].

Despite the increasing interest in the utilization of VR technology, there remains a considerable degree of heterogeneity among health applications. The majority of studies using VR for rehabilitation have focused on addressing motor impairments following a stroke, rather than exploring other rehabilitation objectives or types of brain injuries [10,12]. Furthermore, it is noteworthy that the most commonly used output devices are flat screens and older-generation headsets [16]. Since the introduction of the first high-end fully immersive VR-based system commercially available in 2016 (ie, Oculus Rift [21]; Oculus VR), only a handful of studies have provided robust evidence regarding the feasibility and efficacy of new-generation immersive devices in rehabilitation [22-24]. Most reviews have indicated that the limited evidence stems not from negative or inconclusive outcomes, but from a deficiency in methodological designs that yield high-quality evidence levels [16,25]. As a result, determining whether the benefits of VR-based interventions are clinically significant remains challenging [26]. Therefore, VR-based interventions are still in the early stages of full implementation within real hospital settings. Establishing a standard operating procedure would prove beneficial for enhancing reproducibility, facilitating comparison, and promoting the generalization of findings across studies.

Recent recommendations regarding the utilization of VR-based interventions for clinical applications emphasize the significance of implementing a phased approach design for new programs, which includes conducting pilot studies to assess usability [27,28]. The customization of tasks to cater to the specific needs of individuals, along with the integration of serious gaming techniques [29], represents key advantages of VR in promoting effective neurorehabilitation [30-32]. Serious games techniques encompass various strategies such as adjusting the intensity and complexity of tasks, integrating multisensory feedback, using avatar representations, reinforcing actions with sound effects, and rewards. These techniques aim to foster a high level of engagement and sustain individual focus and motivation during rehabilitation sessions [33]. Moreover, they contribute to enhancing neuroplasticity through repetitive training, as highlighted by research studies [18,34,35].

The most recent studies on VR interventions for cognitive rehabilitation following ABI have focused on conducting detailed design and prototype evaluations of self-developed systems [36,37]. These studies underscore the significance of integrating expertise from cross-disciplinary perspectives, which has resulted in high levels of user satisfaction and low levels of simulator sickness. Additionally, the authors conducted second-phase trials to effectively evaluate the feasibility and preliminary efficacy of the VR-based intervention. Their primary findings suggest improvements in outcome measures of cognitive functions when the intervention is tailored to address the specific cognitive function, incorporating serious games techniques, using a patient-centered design approach, and administering sessions lasting approximately 30 minutes each [38-41].

Objectives

This study aims to address the aforementioned recommendations by prioritizing the early engagement of both patients and clinicians in the development process. The approach involved the co-design of a new VR-based cognitive rehabilitation support tool, which underwent iterative system testing to elicit requirements and establish its utility, safety, and viability before progressing to large-scale studies. The co-design process included active participation from end users and a range of health professionals, including physical medicine and rehabilitation physicians, neuropsychologists, occupational therapists, physiotherapists, as well as researchers and technologists. The objective was to ensure the usability and feasibility of a fully immersive VR-based cognitive rehabilitation support tool among individuals with ABI through a multiple proof-of-concept study. This insight was crucial for formalizing the specific requirements for integrating VR into the daily practice of real hospital settings. The findings from this study may serve as a road map for developing new VR tools in this field and lay the groundwork for future high-quality studies. These studies are essential to ascertain the real efficacy and cost-effectiveness of VR-based interventions in clinical practice.

Methods

Overview

The methodology of this study comprised 2 main parts. First, the design and development of a VR-based cognitive rehabilitation support tool, which followed a thorough and iterative approach involving a multidisciplinary team from the Institut Guttmann, a specialized neurorehabilitation health care center. Second, patients with ABI were recruited to participate in a single session using the VR-based system within the real hospital setting, aimed at assessing the usability and feasibility of the proposed intervention.

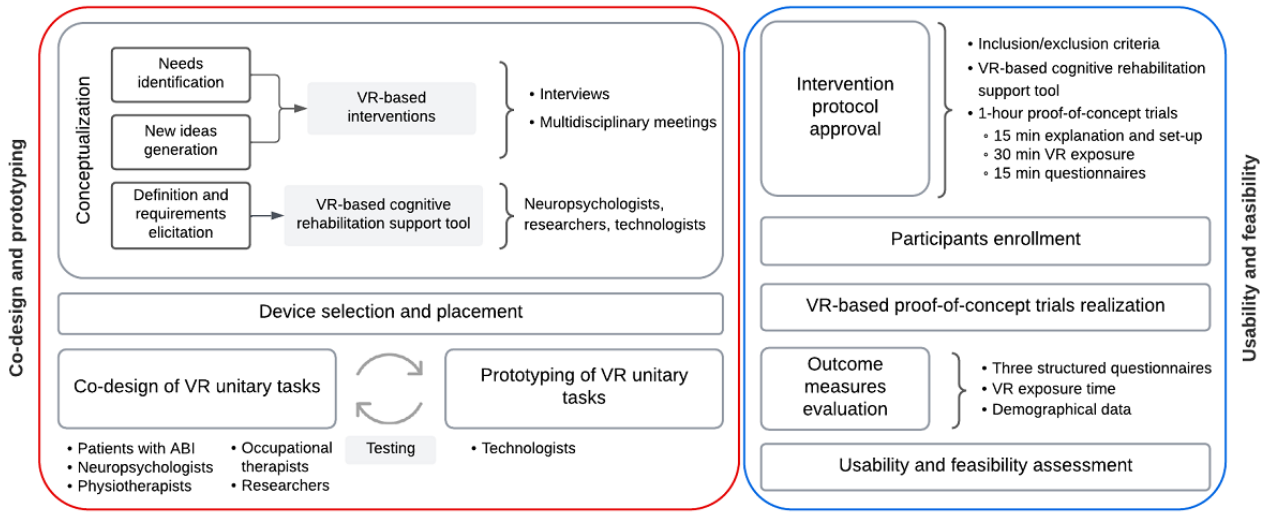
Study Design

In the first part, the need for acquiring a VR-based support tool was identified through interviews conducted with clinical professionals involved in the neurorehabilitation process (for detailed information, refer to Table S1 in Multimedia Appendix 1). Subsequently, a multidisciplinary team brainstormed new ideas for VR-based interventions and suggested the development of a novel cognitive rehabilitation support tool. The acquisition of a modern VR headset was planned, and strategic placement was arranged within the hospital configuration to facilitate its use. Researchers, neuropsychologists, and technologists

commenced work on a phased co-design and prototyping of VR tasks targeting specific cognitive functions. These prototypes underwent testing in close consultation with the multidisciplinary team and patients with ABI. Feedback was collected, and corresponding changes were implemented for each task iteratively until maximum safety and desired functionality were ensured.

The second part involved conducting a multiple proof-of-concept study to evaluate the usability and feasibility of the self-developed VR-based cognitive rehabilitation support tool in patients with ABI (Figure 1). Participants were recruited from the Institut Guttmann.

Figure 1. Study design methodology description, divided into 2 main parts: the co-design and prototyping phase and the usability and feasibility phase. ABI: acquired brain injury; VR: virtual reality.



Ethical Approval

Ethical approval for this trial was obtained from the Ethical Research Committee (CEIm) of the Fundació Unió Catalana d'Hospitals (reference number CEI 22/34), and the study was conducted in compliance with the principles outlined in the Declaration of Helsinki. Written informed consent forms were completed by all participants.

Participants

Various profiles participated in the co-design and prototyping phase (refer to Table S2 in Multimedia Appendix 1). The initial cross-disciplinary team comprised 9 research members from the Institut Guttmann, including 3 neuropsychologists, 2 physiotherapists, 2 technologists, and 2 researchers in the field of technological innovation applied to health. Together, they developed the initial approach for the VR-based tool.

After the initial prototypes were developed and tested by the research team, additional clinical professionals, including physiotherapists, occupational therapists, and neuropsychologists, were invited to test advanced prototypes. They were asked to provide feedback as they familiarized themselves with manipulating the tool.

The most advanced prototypes, which met acceptable safety levels based on clinical criteria, were tested by 9 patients of varying ages and sexes, spanning from childhood to youth to advanced age, and with different etiologies including TBI, stroke, or brain tumor. These patients were undergoing functional training at the rehabilitation gym of the Institut Guttmann. They were required to understand basic instructions, possess sufficient mobility to manipulate a controller with at least one hand, not have epilepsy or vertigo, and be capable of wearing glasses if needed. Positive feedback was appreciated, and valuable comments and observations were collected to inform the final acquisition of the VR-based cognitive rehabilitation tool.

For the usability and feasibility assessment, all individuals admitted to the Institut Guttmann between June and August 2022 were considered for participation in the multiple proof-of-concept study if they met the following criteria:

- Presence of an ABI (moderate to severe TBI, stroke, or brain tumor).
- Age equal to or greater than 16 years.
- Presence of cognitive impairment assessed using a neuropsychological test battery.
- Well-oriented in the 3 different spheres (person, space, and time) and understands basic instructions.
- Had enough mobility to manipulate a controller with at least one hand and press any button.
- Received cognitive rehabilitation training through a not-immersive computer-generated tool named Guttmann NeuroPersonalTrainer [42].

The exclusion criteria were as follows:

- Presents linguistic (aphasia) or visuoperceptive alterations that could affect the administration and validity of the results obtained in the neuropsychological assessment battery or VR session performance.
- Psychiatric or neurological history before ABI.
- Have epilepsy or disorders associated with motion sickness.
- Patients with skull shape abnormalities who cannot comfortably hold the VR headset.

During the recruitment period, a total of 20 inpatients (9 female) met the inclusion criteria and were enrolled in the study. Among them, 7 patients had a TBI, 12 had a stroke, and 1 presented with a brain tumor.

VR System

Device and Development Tools

The VR system must possess the capability to capture user actions through motor interfaces. These actions will be interpreted as requests to modify the virtual environment and sensory reactions will be transferred to the sensory interfaces. Furthermore, specific hardware capabilities, including the type of display screen, resolution, image refresh rate, and field of view, along with software attributes such as ergonomic interactions and navigation, are crucial for mitigating VR-induced symptoms and effects [43,44]. The minimal technical specifications for such a system are listed in Table 1.

Table 1. VR[a] device minimal technical requirements specification.

Object	Requirement
Display screen	OLED[b] or LCD[c]
Screen resolution	>960 × 1080 pixels per eye
Refresh rate	≥75 Hz
Field of view	≥110° diagonal
Audio	Integrated and adjustable
Sensors	6-DoF[d] tracking, accelerometer, gyroscope, proximity, and haptic
Ergonomics	Adjustable eye comfort setting (IPD[e]); head strap
Tracked area	Up to 2 m × 2 m
Controllers	Minimum of 2 with buttons and 6 DoF

[a]VR: virtual reality.

[b]OLED: organic light emitting diode.

[c]LCD: liquid crystal display.

[d]DoF: degrees of freedom.

[e]IPD: interpupillary distance.

The HTC VIVE Pro Eye (HTC Corporation) [45], a new-generation high-end HMD and handheld controller, was selected and integrated into the hospital configuration. This device is currently commercially available in most countries and is compatible with industry-standard interfaces such as SteamVR (Valve Corporation) [46] and OpenVR (Valve Corporation) [47]. With the Unity3D (Unity Technologies) game engine [48], our team successfully created immersive, interactive, and true-to-reality virtual environments. These environments can be executed on any VR station that meets the aforementioned minimal technical requirements.

From Prototyping to Immersive Serious Games

A co-design approach was undertaken involving health professionals, researchers, and technologists. The multidisciplinary team engaged in discussions regarding the configuration of the VR session, addressing aspects such as duration, the number of tasks, task characteristics, and measurable data. Recognizing that individuals with ABI may have disabilities across multiple areas of functionality, the team emphasized the importance of developing a set of unitary tasks. This approach would allow for targeting different cognitive abilities and obtaining relevant outcomes separately, thereby ensuring comprehensive training for the patient.

Unitary tasks should be designed to be achievable, with clear objectives, and customized based on each patient's specific needs to accommodate any physical or cognitive limitations they may have (eg, muscle rigidity or hypersensitivity). Participants could use 1 or 2 handheld controllers, and interactions were simplified by programming multiple buttons to perform the same action.

Tasks could be completed in either sitting or standing positions; however, to minimize the risk of falling, as reported in a previous study [49], all participants underwent the VR session while seated. Accelerations or decelerations were avoided and substituted with uniform linear motion or teleporting methods to ensure a safe and comfortable experience for the participants. This approach reduces motion sickness by requiring users to actively control their viewpoints and be responsible for initiating movement [18]. Virtual scenes were designed to be as realistic as possible, corresponding to the stimulus type (eg, a sports center for football stimuli), and the stimuli appeared within the user's field of view. All exercises followed a dual-task approach, incorporating both cognitive and motor cues (eg, reaching visuospatial stimuli), to provide a comprehensive rehabilitation experience.

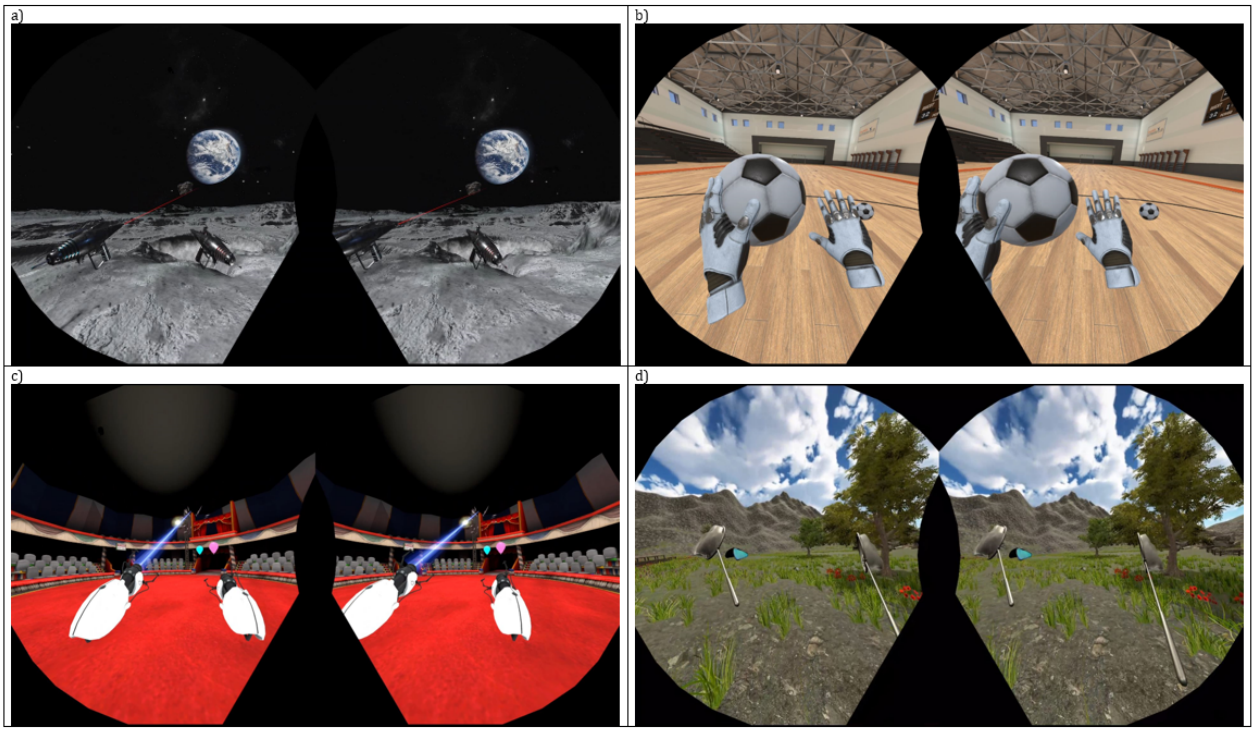
The final prototypes were attained through continuous testing and evaluations involving end users and clinical professionals. Key topics and features that underwent extensive discussion and redesign were game mechanics, interactivity, sound effects, graphic design, and variable thresholds to delineate difficulty levels. Seven immersive experiences were developed, addressing

3 different cognitive functions: attention (n=4), memory (n=1), and executive functions (n=2).

Prototyping these experiences as serious games facilitated the incorporation of appropriate feedback, including visual (V), auditory (A), and haptic (H) cueing. This approach enabled the provision of instructions, rewarding or annoying stimuli to guide users in expected motion realization, and the ability to display or perceive real-time performance results [50]. The emission of slight vibrations when interacting with a virtual object can induce the sense of having touched it. Additionally, task difficulty was adjusted to fit the patient's therapeutic window, allowing the professional to select 1 of 3 possible difficulty levels. Each task automatically modified certain dependent variables based on the chosen difficulty level.

Attentional serious games consist of 4 visuospatial tasks (Figure 2). Each task involves a different presentation-interaction approach: (1) stimuli moving at different constant speeds from right to left in a straight line and then reversing direction at different heights. The user, who is stationary, must shoot them; (2) stimuli moving toward the user in a parabolic arch trajectory from different positions. The user must intercept them; (3) stationary stimuli distributed at various points within the user's field of view. The user must shoot them; and (4) stationary stimuli appearing near the user's left or right side while they are virtually moving forward at a constant low speed. This creates the perception that the user is moving toward the stimuli and can reach them with their hands.

Figure 2. The 4 attentional immersive serious games: (A) Moon, (B) Goalkeeper, (C) Circus-I, and (D) Butterflies.



One memory task was developed to train short-term and working memory within an immersive 3D naturalistic environment (Figure 3). Users could focus on the exercise they had to carry out without any external distractions. The task comprises 3 phases: an encoding phase, an interference phase (which can be configured as maximum or minimum interference), and a decoding phase.

The executive function tasks aim to train high-level cognitive abilities, such as planning, problem-solving, and decision-making. For this research, 2 tasks were developed wherein the participant is immersed in performing a repetitive task that varies in the principal instruction that must be carried out (Figure 4). The first task follows the design of a sequence imitation task, while the second exercise was designed to control automatic responses using attention and reasoning through an inhibitory control task.

During VR sessions, in-game measures were collected, including time stamps, hits/failure scores, reaction times, user-system interactions, gaze/position tracking data, and stimuli data. At this stage, an easy-to-use system with a quick set up for sessions involving a set of VR experiences addressing cognitive functions was achieved.

Figure 3. A memory immersive serious game (Totem) and its phases: (A) encoding, (B) min-interference, (C) max-interference, and (D) decoding.

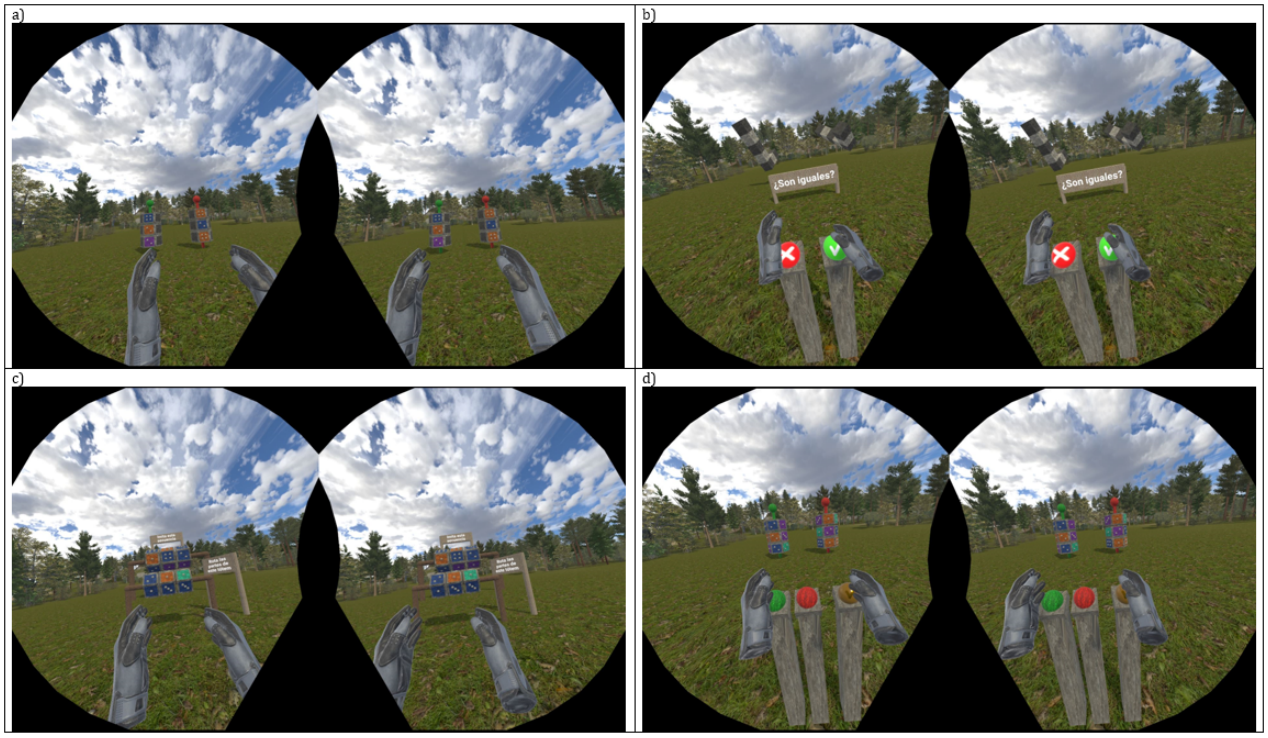
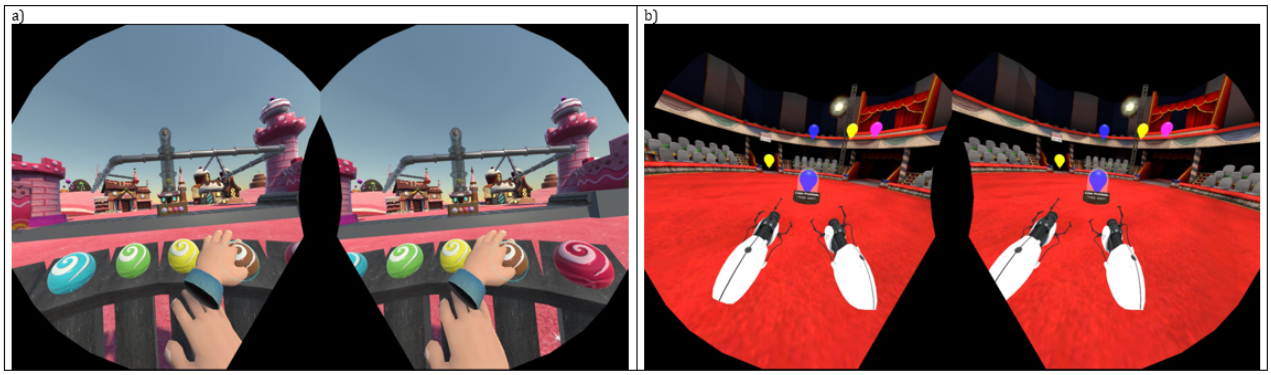


Figure 4. The 2 executive functions immersive serious games: (A) Conveyor-belt and (B) Circus-II.



Intervention

Immersive serious games were deployed on the HTC VIVE Pro Eye device, which was equipped with 2 room tracking units (infrared cameras) and 2 controllers. Once the doctor identified a potential participant, he/she or a tutor was invited to participate in the study. Enrolled patients substituted 1 hour of their cognitive treatment with traditional cognitive rehabilitation therapy with 1 hour of intervention using the VR-based system tool. All sessions were conducted between June and August 2022.

During the initial 15 minutes, the participant completed the informed consent forms and was seated in a chair or positioned in their wheelchair in a designated area within the VR system's tracking zone. To ensure safety, clear space within the room was maintained, keeping the participant at a distance from any objects or individuals to prevent collisions. Subsequently, the VR headset and controllers were placed on the participant. The treatment provider configured the VR session via a host computer by selecting the difficulty level for each cognitive category (hard, medium, or easy) and specifying the hands involved (see photos of the set up in Multimedia Appendix 2).

The session consisted of completing various tasks, with each task lasting 4-6 minutes. The total intervention time wearing the headset was approximately 30 minutes unless the patient requested to conclude earlier. The intervention time was calculated as the sum of the duration of each task carried out, excluding the time elapsed between tasks when the treatment provider ensured that the task objectives were understood and instructed the patient on how to interact with the environment. The number of total tasks performed was also counted. When there were 15 minutes remaining until the end of the VR session, the HMD was removed, and questionnaires were administered to participants to assess their overall user experience.

Outcome Measures

To assess the usability and feasibility of the VR-based support tool for cognitive rehabilitation in patients with ABI, 3

structured questionnaires were used (Table S1 in Multimedia Appendix 3). Additionally, information regarding the optimal dose of treatment and patients' age, based on the duration of time spent performing VR tasks, along with demographic data, was collected.

The first questionnaire comprised a 5-point Likert scale, ranging from "5=fully agree" to "1=fully disagree," assessing system usability and acceptance based on the participant's perception. The responses were related to the sense of presence, dimensions matching, the ability to see and differentiate objects, interactivity, task specificity, task difficulty, motivation, enjoyment, and errors. Following this, 3 questions were posed regarding the frequency (on a 5-point Likert scale, ranging from "5=all the time" to "1=never") of using various new technologies to gauge the familiarity level. Finally, the Simulator Sickness Questionnaire (SSQ) [51] was used to evaluate side effects by measuring users' level of sickness symptoms such as nausea (N), oculomotor problems (O), and disorientation (D). Each of the 16 items in the SSQ is rated on a 4-point scale: 0 (none), 1 (slight), 2 (moderate), and 3 (severe). Participants were instructed to indicate the severity of each symptom they experienced during or after the VR exposure by selecting the appropriate rating for each item.

For the Usability Questionnaire (UQ) and the Technology Familiarity Questionnaire (TFQ), the value for the "worst" condition answer will count as 0, and the value for the "best" condition answer will count as 4. As the UQ has 10 questions, the maximum total score can be 40. A higher usability score indicates that the system is more useful and feasible for implementation in a hospital setting for patients with ABI during neurorehabilitation. The maximum total score for the 3-question TFQ can be 12, indicating a greater acceptance of new technologies.

By contrast, the total score for the SSQ can range from 0 to 48, with significant symptoms indicated by scores between 10 and 15, concern for scores between 15 and 20, and scores over 20 indicating a problem with the simulator. Their usage permitted detailed analysis of the distribution of nausea, oculomotor, and disorientation symptoms elicited by the experimental manipulation. If any score falls within a concerning range, it should be studied separately because this scale was originally designed for military flight simulators and may appear overly strict when applied to nonaviators [52]. However, this questionnaire is one of the most widely used ones for assessing cybersickness in immersive VR rehabilitation [53]. Thus, its use allowed for comparison with previous research.

Structured questionnaires containing numbered questions, accompanied by keywords pertaining to usability, technical familiarity, and side effects, along with the complete question sentences, are available in Table S1 in Multimedia Appendix 3.

Statistical Analysis

We aimed to recruit enough inpatients with ABI to identify all usability problems in the design [54] and the early stage of this self-developed VR tool and to gather sufficient data to estimate the SD of measured outcomes for planning a subsequent larger trial [55]. Recent studies, which involved new-generation headsets, customized VR-based rehabilitation tools, focused on patient needs, tested the system in samples ranging from 11 to 35 patients with ABI, and found that VR was accepted and feasible for rehabilitation [37,38,56].

Descriptive analyses were conducted to establish recruitment, acceptance, and completeness, using demographic information, questionnaire scores, measures of intervention duration, and the number of tasks completed. Descriptive statistics data from participants with TBI and stroke were reported separately. As only 1 participant had a brain tumor, their data were not included in the etiology-group comparison. However, their data were included in the age-group comparison established for future eligibility criteria.

The calculations were conducted using Microsoft Excel. The R package (R Foundation) *corrplot* [57] was used to graphically represent the scores obtained in the questionnaires and compare them according to age and etiology. Additionally, the same package was used to explore the correlation matrix between SSQ subscale symptoms, usability categories, technology familiarity, in-game measures, and some demographics. *P* values with a significance level <.05 and correlation coefficients (*r*, ranging between –1 and +1) were provided to aid in determining the statistical significance and the direction and intensity of correlations.

Results

Sample Characteristics

A total of 20 inpatients with ABI participated in this usability and feasibility study. The sample mean age was 38.3 (SD 14.1) years, with a mean time since injury (TSI) of 4.7 (SD 1.5) months. The total scores obtained for each of the 3 questionnaires administered (ie, UQ, TFQ, and SSQ) were 37 (SD 2.6), 9.2 (SD 2.9), and 1.3 (SD 2), respectively. Finally, the total mean duration of each intervention across all participants was approximately 25.6 (SD 4.7) minutes, while the number of tasks completed was 5.1 (SD 1).

Among the 7 patients with TBI, 4 reported a severe level of impairment according to the Glasgow Coma Scale (between 3 and 8) [58]. Among the 12 patients with stroke, 7 had ischemic strokes and 4 had hemorrhagic strokes. There were 2 cases of minor stroke according to the National Institute of Health Stroke Score (NIHSS; ranging from 0 to 42: 0, no deficit; minor impairment, 1-4; moderate, 5-15; moderate to severe, 16-20; and severe impairment 21-42) [59]. Seven patients had moderate stroke severity, and 2 presented with moderate to severe stroke. The patient who had a brain tumor underwent surgery for resection of a pituitary macroadenoma.

Patients underwent a battery of neuropsychological tests before being incorporated into the study; 8 of them had alterations in the cognitive function of attention, 8 presented with memory impairment, and 18 had difficulty performing executive functions. Five patients had completed advanced studies (>12 years of schooling), while 8 had an intermediate level of education (between 8 and 12 years of schooling) and 6 completed primary education (<8 years of schooling).

Moreover, one patient presented with hemispatial neglect, 6 had left-side hemiplegia, and 4 had visual-field defects, including homonymous hemianopia, diplopia, or limited gaze.

The individual demographics and some clinical data are reported in Table 2. For more details and complete information, please refer to Table S1 in Multimedia Appendix 4.

Table 2. Individual demographic and clinical data.

Patient code	Age (years)	Sex	Etiology	TSI[a]	NIHSS[b]	GCS[c]
2020342-1	16	Female	TBI[d]	8.7	—[e]	Missing
2020342-2	38	Male	TBI	3.4	—	3
2020342-4	63	Male	TBI	3.9	—	3
2020342-5	48	Male	Ischemic stroke	5.5	18	—
2020342-6	19	Female	Hemorrhagic stroke	4.6	12	—
2020342-7	40	Male	TBI	4.2	—	Missing
2020342-8	41	Male	Hemorrhagic stroke	5.0	2	—
2020342-9	20	Male	TBI	5.3	—	4
2020342-10	19	Female	TBI	5.0	—	3
2020342-11	39	Female	Ischemic stroke	3.5	20	—
2020342-12	32	Female	Hemorrhagic stroke	3.9	2	—
2020342-13	38	Male	Brain tumor	3.1	—	—
2020342-14	25	Male	Ischemic stroke	3.3	7	—
2020342-15	58	Male	Ischemic stroke	6.5	12	—
2020342-16	51	Female	Ischemic stroke	5.5	12	—
2020342-17	29	Female	Hemorrhagic stroke	4.3	Missing	—
2020342-18	50	Female	Ischemic stroke	3.3	14	—
2020342-19	34	Male	TBI	5.4	—	Missing
2020342-20	58	Female	Hemorrhagic stroke	6.9	12	—
2020342-21	47	Male	Ischemic stroke	2.8	5	—

[a]TSI: time since injury (months).

[b]NIHSS: National Institute of Health Stroke Score.

[c]GCS: Glasgow Coma Scale.

[d]TBI: traumatic brain injury.

[e]Not available.

Evaluation of Outcome Measures

We divided participants into separate groups based on etiology (TBI and stroke) and age (young: 16-39 years and adult: 40-63 years). We used appropriate measures of central tendency and variability, such as means and SDs (Table 3). According to each etiology and age subgroup comparison, all of them achieved more than 36 points in the UQ score, very close to the maximum of 40 points. Participant subgroups achieved more than 8 points out of 12 for being experienced in using new technologies such as personal computers, smartphones, and the internet. Regarding the manifestation of motion side effects, none of the groups achieved a minimum of 10 points on the SSQ score, indicating the absence of negative symptoms. A difference of 7.4 minutes was observed when comparing the intervention duration time between the TBI and stroke subgroups. Thus, participants with stroke scored 1 point higher in the TFQ score and completed 1 more task than participants with TBI.

The scores obtained by the participants in the TFQ questionnaire were compared depending on age and separated by etiology, excluding the patient with brain tumor (Figure 5). Most participants reported an acceptable level of the use of new technologies, but 5 achieved scores below half the maximum. The 2 lowest scores, 4/12, were obtained by patients with TBI. One participant, a 38-year-old male with a Glasgow Coma Scale score of 3, obtained the lowest score of 4/12. Another participant, a 40-year-old male with no available severity data, also scored 4/12. The next lowest score of 5/12 was obtained by 2 patients with moderate to severe stroke. One was a 51-year-old woman with an NIHSS of 12, and the other was a 39-year-old woman with an NIHSS of 20. Finally, a score of 6/12 was obtained by a 58-year-old male patient diagnosed with moderate stroke (NIHSS of 12). It is important to highlight that age-matched participants, even older, reported an acceptable use of new technologies.

Table 3. Descriptive statistics of age and TSI[a], results of the UQ[b], TFQ[c], SSQ[d], intervention duration, and number of tasks realized.

Statistic	TBI[e] (n=7), mean (SD)	Stroke (n=12), mean (SD)	Young (n=11), mean (SD)	Adult (n=9), mean (SD)
Age	32.9 (16.5)	41.4 (12.8)	28.1 (8.7)	50.7 (7.8)
TSI	5.1 (1.7)	4.6 (1.3)	4.6 (1.6)	4.8 (1.4)
UQ	37.4 (1.7)	36.8 (3.1)	36.5 (3)	37.6 (1.9)
TFQ	8.4 (3.3)	9.4 (2.8)	9.5 (2.8)	8.9 (3.3)
SSQ	0.9 (1.9)	1.4 (2.3)	1.5 (2.4)	1 (1.6)
Duration	20.9 (3.8)	28.3 (2.8)	26.2 (3.9)	25 (5.7)
N_tasks	4.4 (1)	5.4 (0.8)	5.4 (0.9)	4.8 (1)

[a]TSI: time since injury.

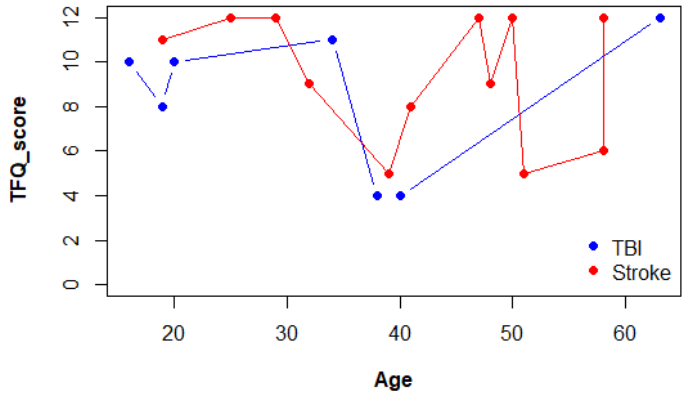
[b]UQ: Usability Questionnaire.

[c]TFQ: Technology Familiarity Questionnaire.

[d]SSQ: Simulator Sickness Questionnaire.

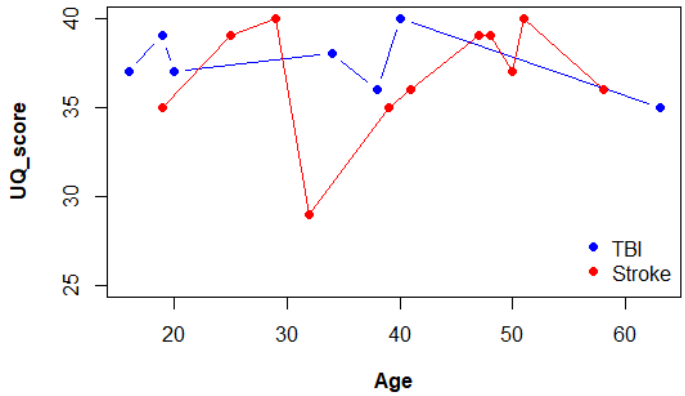
[e]TBI: traumatic brain injury.

Figure 5. Comparison plot between TFQ scores obtained by etiology and distributed by age. TBI: traumatic brain injury; TFQ: Technology Familiarity Questionnaire.



The mean tech familiarity score for patients with stroke (9.4) was slightly higher compared with that for patients with TBI (8.4), but this did not affect the usability scores. Overall, all participants achieved high usability scores, equal to or over 35/40, except for 1 patient, a 32-year-old woman diagnosed with a minor stroke (NIHSS of 2), who scored 29/40 points for the usability of the VR intervention (Figure 6). This could be because the patient consistently rated all questions with a 4/5, instead of assigning lower scores to some items. Additionally, she appeared indifferent regarding the occurrence of errors, as evidenced by consistently assigning a score of 3/5.

Figure 6. Comparison plot between UQ scores obtained by etiology and distributed by age. TBI: traumatic brain injury; UQ: Usability Questionnaire.



When comparing the spatial distribution of the stroke and TBI subgroups based on age, no substantial differences were observed regarding usability, by either age or etiology.

Similarly, in terms of simulator sickness, neither the 2 etiology groups nor the patient with a brain tumor (SSQ score=2) exhibited any substantial differences in the presence of symptoms, regardless of age (Figure 7). The upper limit of the

y-axis, as shown in Figure 7, has been truncated at 10. This range ensures safety by indicating the absence of simulator sickness. None of the patients obtained a score greater than this threshold.

Another aspect under examination is the duration of the VR-based intervention while wearing the headset. Following the time needed for patients to understand the intervention, fit and set up the equipment, and complete questionnaires, all participants were allotted approximately 30 minutes to engage in a series of immersive serious games. The subgroup of patients with stroke appeared to tolerate longer interventions wearing the headset compared with patients with TBI because, on average, the stroke subgroup performed more tasks. Additionally, Figure 8 illustrates a decreasing trend in the duration of VR interventions with older ages for patients with TBI.

Figure 7. Comparison plot between SSQ scores obtained by etiology and distributed by age. SSQ: Simulator Sickness Questionnaire; TBI: traumatic brain injury.

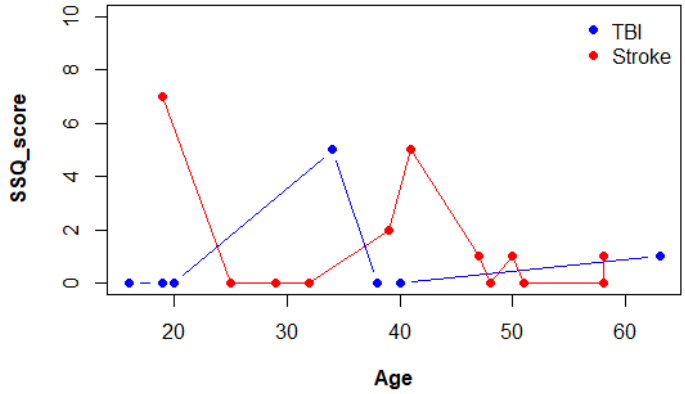
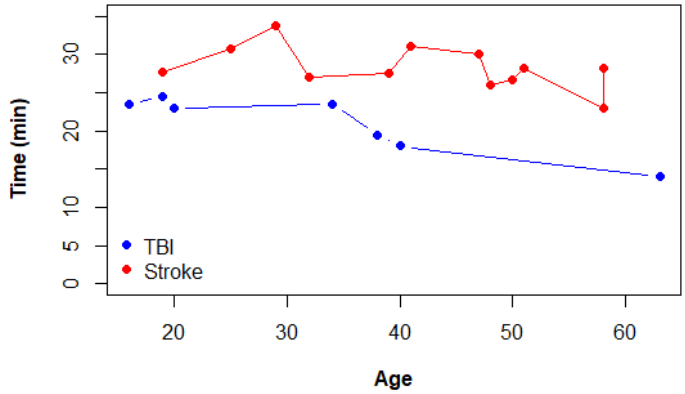


Figure 8. Comparison plot between intervention duration time differentiation by etiology and age.



The sample size of participants with TBI was small, but several factors may contribute to explaining these differences in time exposure. First, 2 participants with TBI completed a set of 5 tasks more quickly than those with stroke, possibly because they were on average 10 years younger (see Table S2 in Multimedia Appendix 4). According to the literature, younger age correlates with faster reaction times [60]. By contrast, an adult participant with TBI (code 2020342-19) reported feelings of dizziness and pixelated vision (see Table S2 in Multimedia Appendix 3). He stopped mid-intervention to remove the VR glasses and rest for a couple of minutes. Additionally, the oldest patient in the entire sample was from the TBI subgroup and was the one who requested to finish early, completing only 3 tasks. These occurrences contributed to a shorter intervention time for the TBI subgroup.

Based on this rationale and observing the result of the comparison between UQ scores and TFQ scores (Figure 9), the co-designed and developed VR-based cognitive rehabilitation support tool appears to be feasible when applied in the hospital setting and with patients with ABI. It demonstrates high usability regardless of age, the origin of the lesion, and familiarity with new technologies.

We also investigated the correlations among Simulator Sickness subscale symptoms, usability categories, tech familiarity scores, age, TSI, number of tasks performed, and time wearing the VR headset (Figure 10). The intensity of the square's color is directly proportional to the strength of the correlations between variables. Positive correlations are labeled with cool colors, whereas negatives are warm. Significant correlations are indicated with asterisks. The exact *P* values are presented in Table S1 in Multimedia Appendix 5.

Figure 9. Comparison plot between UQ and TFQ scores, separated by etiology. TBI: traumatic brain injury; TFQ: Technology Familiarity Questionnaire; UQ: Usability Questionnaire.

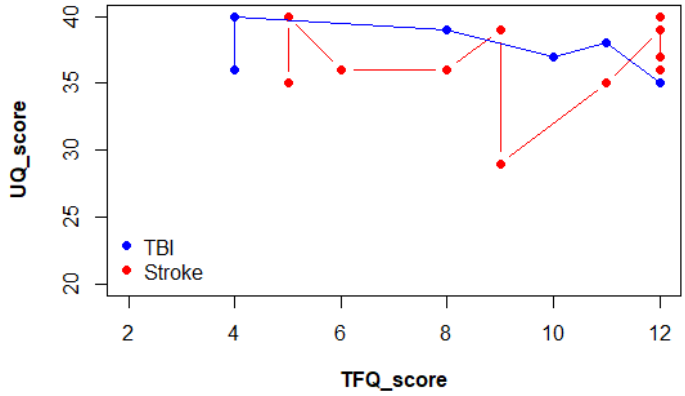
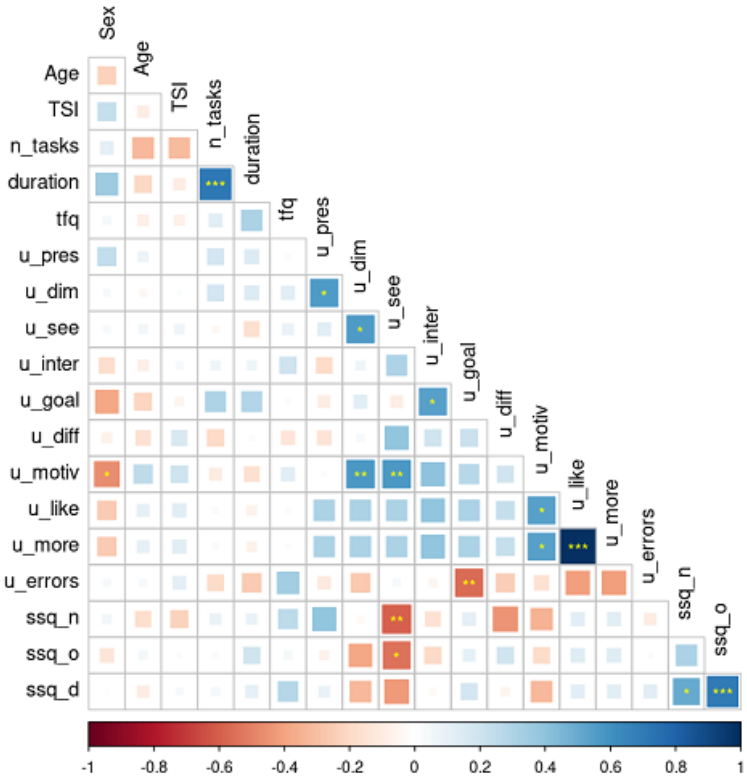


Figure 10. Correlations between sample's demographic characteristics, number of tasks completed, session duration time, technology familiarity, usability categories, and SSQ. *P<.05, **P<.01, and ***P<.001. SSQ: Simulator Sickness Questionnaire; TFQ: Technology Familiarity Questionnaire; TSI: time since injury.



There were significant, strong correlations between some variables included in the analysis. The data extracted from the session performance were closely related, and therefore, the intervention duration positively correlated with the number of tasks performed (r=0.72, P<.001), as expected. Regarding usability categories, the dimensions matching (u_dim) correlated with the sense of presence (u_pres: r=0.56, P=.01) and with the ability to see and differentiate objects (u_see: r=0.56, P=.01). The task goal-specificity (u_goal) correlated positively with the ability to interact with the environment (u_inter: r=0.55, P=.01). The motivation prompted by the intervention (u_motiv) correlated with the dimensions matching (u_dim: r=0.57, P=.008) and with the ease in seeing and differentiating objects (u_see: r=0.57, P=.008). Additionally, motivation correlated with sex, considering that 0 corresponds to the male sex and 1 to the female sex. As the sign of the correlation is negative, a strong correlation between male sex and motivation was observed (r=–0.46, P=.04) [61]. Furthermore, the liking of VR interventions (u_like) and the desire to conduct more VR in rehabilitation programs (u_more) were correlated (r=0.56, P<.001), and both were also correlated with the motivation experienced (u_motiv) with similar results (r=0.55, P=.01). The presence of errors that some participants had reported correlated negatively with the ability to understand and achieve the goal of the task (r=–0.56, P=.009).

Finally, concerning the SSQ symptoms analyzed, a strong correlation between disorientation (ssq_d) and oculomotor problems (ssq_o) was observed (r=0.71, P<.001). The disorientation sickness symptoms also correlated with the nausea sickness symptoms (ssq_n: r=0.50, P=.02). Additionally, the nausea symptoms and oculomotor problems negatively

correlated with the ease in seeing and differentiating objects (r=–0.60, P=.005 and r=–0.54, P=.01, respectively).

Discussion

Support Tool Developed

The VR-based support tool proposed in this study comprised a high-end new-generation commercial device, namely, the HTC VIVE Pro Eye, along with a series of custom tasks designed to rehabilitate cognitive functions (eg, attention, memory, and executive functions) in patients with ABI. These patients were undergoing neurorehabilitation treatment at a health care center. The overall satisfaction percentage achieved by the sample of 20 patients, considering the usability score and the evaluation of side effects, was 89.8% (431/480; 37/40 usability points, subtracting 1.3 from 48 SSQ points). The system was developed following recent recommendations [27,28] combined with our approach to how VR applications should be designed for clinical trials (Textbox 1). The results obtained from this study may contribute to filling the gap in the literature related to the lack of studies that follow a methodological process of best practices to integrate VR technology as a neurorehabilitation support tool for patients with ABI in the daily practice of real hospital settings [24,25,62].

Textbox 1. Stepwise summarized approach to achieve a virtual reality–based neurorehabilitation support tool for inpatients with acquired brain injury.

1. **Identification of virtual reality (VR)–based intervention needs and barriers for patients with acquired brain injury (ABI)**
   - A multidisciplinary meeting involving health professionals and researchers identified the need for a VR-based neurorehabilitation support tool for patients with ABI.
   - Difficulties and barriers were identified, and possible solutions were proposed, in collaboration with technologists and VR experts.
   - The first approach to VR support tool features and treatment interventions was defined.
2. **Selection and placement of technological device**
   - A high-end new-generation immersive system was selected and placed within the hospital setting.
   - Device testing with available off-the-shelf VR games was conducted with clinical professionals and end users.
3. **Co-design of VR-based neurorehabilitation support tool**
   - Physical medicine and rehabilitation physicians, neuropsychologists, therapists, and nurses targeted the patient population and desired intervention.
   - Ideas for new VR experiences were generated, addressing different cognitive or sensorimotor functions.
   - Researchers and developers created the first sketches based on technology capabilities and current knowledge.
   - Immersive serious games, rehabilitative principles, game mechanics, interactions, sound and effects, graphic environment, and measurable data, among other features were discussed.
4. **Prototyping**
   - Developers built prototypes, which were tested and redesigned by co-designers until desired behavior and appearance, maximum safety, easy, and a quick set up were guaranteed.
   - Input and output variables with configurable thresholds were determined.
   - Approaches to minimize cybersickness symptoms, simplified interactions, and multisensory feedback incorporation were used.
   - Use cases were performed involving treatment providers and end users.
   - A set of immersive serious games, including neurorehabilitation principles, was achieved.
5. **Usability and feasibility study**
   - A study protocol was defined, including participant characteristics (inclusion/exclusion criteria), intervention, and outcome measures.
   - Target patients were recruited.
   - Multiple proof-of-concept studies were conducted.
   - Demographics, clinical data, in-game measures, and structured questionnaire responses were collected.
   - Statistical analyses were performed, and results were discussed.
6. **Basis for future research**
   - Requirements of the VR support tool for patients with ABI were elicited.
   - The foundation was established for future large study designs to determine the efficacy of VR interventions.

Principal Findings

Our systematic approach to developing a VR-based neurorehabilitation support tool for inpatients with ABI has resulted in a set of 7 cognitive tasks specifically designed to address the needs of this population. The sample of 20 patients, with a mean TSI of 4.7 (SD 1.5) months, volunteered to participate in assessing the usability and feasibility of the proposed intervention. Participants completed an average of 5 tasks during a single VR session lasting approximately 25 minutes. The set of cognitive tasks was well-received by participants, irrespective of etiology, age, or tech familiarity.

What was significant in this study regarding the achievement of the VR tool and subsequent intervention was the step-by-step approach with the participation of stakeholders throughout the entire process, from design to prototyping, and usability and feasibility assessment. By applying this methodology, we have demonstrated the potential of integrating VR into clinical practice. This supports recent literature findings that also describe detailed customized VR rehabilitation tools and have conducted large-quality studies obtaining promising results [36,39-41,63,64]. All participants from the multiple proof-of-concept study completed the session without experiencing adverse effects or encountering major issues. By targeting multiple areas of functionality, patients can benefit from a more comprehensive and personalized rehabilitation program, which can promote neuroplasticity and potentially improve overall functional outcomes [14,30].

The results demonstrated that when patients enjoyed the tasks, their motivation increased; eventually, they expressed a desire to participate in more VR sessions as part of their rehabilitation programs. This engagement was correlated with a high sense of presence, the ability to perceive and differentiate objects within the virtual environment, and a perception of real-world scale [32,65]. The study also demonstrated that when interactions are customized to fit the abilities of individual patients, their performance in completing the required tasks improves, resulting in greater clarity and specificity of the intended goal [20]. However, when tasks contain errors, it becomes more challenging for patients to understand and achieve the objectives. For example, one patient (code 2020342-2) reported difficulty in hitting the mark when shooting stimuli. This issue will be addressed by incorporating a laser pointer for future studies.

When evaluating cybersickness effects, a strong correlation was observed between patients reporting disorientation and the presence of oculomotor problems and nausea symptoms. This indicates that an increase in one of these symptoms tends to coincide with an increase in the others [49]. Furthermore, when patients reported experiencing nausea symptoms or oculomotor problems, their ability to see and differentiate objects within the scene decreased. Despite the correlations found, the overall average score for the SSQ does not exceed 1.3 points, with a maximum of 1.5 points in the subgroup of young patients (up to 39 years old). This score is still far from the threshold of 10 points, beyond which cybersickness symptoms can cause problems.

There is a demographic correlation between sex and motivation, indicating that men found the VR session more motivating than women [61]. No significant correlation was observed with the age variable. This finding, together with the comparisons of descriptive statistics, may support the evidence that VR is a useful and viable tool for different age groups, ranging from 16 to 63 years old. However, it is important to interpret these findings with caution, as the sample size is not sufficiently large, and only 1 session has been tested, rather than a long-term intervention with a follow-up assessment.

The commercial device selected was suitable for inpatient rehabilitation, in accordance with previous studies [44,66,67]. The headset ensures comfort, improved visual quality, and exposure to graphics, along with selectable handheld controllers, a precise tracking system, and portability. Moreover, the headband and facial interface that come into contact with the patient can be replaced to reduce the risk of spreading infection among patients sharing the same device. The screen, other parts of the headset, and controllers can be disinfected using hydroalcoholic gel. Successful integration of the device within hospital settings, without hindering the use of other rehabilitative tools or treatment programs, is assured. As for the economic feasibility of acquiring the proposed system, both SteamVR and OpenVR software components are freely available for use. The Unity3D game engine provides various licensing options, including a free version. The necessary hardware comprises the following: (1) a mid-range gaming personal computer equipped with a VR-ready graphics card, priced between €1000 (US $1081) and €3000 (US $3244); (2) a high-end VR input/output device such as Valve Index or Oculus, typically priced around €1200 (US $1297); and (3) potential expenses may arise from hiring developers or subcontractors to create the virtual environments.

Limitations

While our study offers valuable insights into the utilization of VR-based tools for cognitive rehabilitation in patients with ABI, it is important to acknowledge several limitations that warrant attention. Primarily, there exists a discrepancy in the number of tasks targeting each cognitive domain. Despite this variance, it is crucial to emphasize that the obtained results were adequate for identifying and delineating crucial aspects of feasibility and usability. Future studies assessing efficacy should encompass a balanced array of tasks targeting each cognitive domain. This approach will facilitate more comprehensive and intensive interventions, addressing the spectrum of cognitive impairments observed in patients with ABI.

In line with this, it would be compelling to broaden our intervention to encompass other realms of rehabilitation, such as upper and lower limb function, gait analysis, mirror therapy, and pain management, among others.

Another limitation is the absence of a centralized server for gathering output variables generated by each task. For future studies aiming to obtain efficacy results, ascertain which data trigger changes during the neurorehabilitation process, and develop predictive models to personalize treatments, having such a server would be invaluable.

Furthermore, certain patients' clinical records contained missing data regarding the severity scales, potentially affecting the analysis of results. The complete tables, encompassing all collected variables including individual responses to questionnaires, are available for reference in Multimedia Appendices 3 and 4.

Finally, although the design and refinement of the VR experiences were conducted by a multidisciplinary team comprising health professionals and end users, structured questionnaires were not administered to them during this process. However, a log detailing meetings, tests conducted, the primary themes explored, alterations made, error corrections, and some feedback was prepared (see Table S1 in Multimedia Appendix 1).

Conclusions

Based on our understanding, this study holds significance as it lays the foundation for a VR-based neurorehabilitation support tool applicable to a wide spectrum of patients with ABI within the practical context of a hospital setting. The process of requirement elicitation and iterative development was meticulously conducted in collaboration with a multidisciplinary team, aligning closely with the latest recommendations from the literature.

This study provides evidence demonstrating the utility and feasibility of VR-based treatments when tailored to meet the specific needs of a targeted patient population. It underscores the significance of collaborative intervention design involving physicians, physiotherapists, neuropsychologists, occupational therapists, nurses, researchers, technologists, and incorporating patient perspectives. The intervention ought to encompass a diverse range of immersive experiences, drawing upon neurorehabilitation principles and serious games techniques while ensuring ecological validity. By adhering to this approach, VR-based interventions hold the potential to provide valuable support in neurorehabilitation settings.

Future studies should aim to conduct rigorous research with larger sample sizes and robust study designs to offer more substantial evidence regarding the clinical value and cost-effectiveness of VR-based interventions in the neurorehabilitation of patients with ABI. For this purpose, a clinical efficacy study is already in progress. The ultimate objective is to develop a standard operating procedure that facilitates reproducibility, comparison, and generalization of findings.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
VR-based support tool acquisition procedure. VR: virtual reality.
[PDF File (Adobe PDF File), 281 KB - neuro_v3i1e50538_app1.pdf]

Multimedia Appendix 2
Setup photos.
[PDF File (Adobe PDF File), 592 KB - neuro_v3i1e50538_app2.pdf]

Multimedia Appendix 3
Questionnaire models and results.
[PDF File (Adobe PDF File), 278 KB - neuro_v3i1e50538_app3.pdf]

Multimedia Appendix 4
Demographic and outcome measures data of the sample.
[XLSX File (Microsoft Excel File), 14 KB - neuro_v3i1e50538_app4.xlsx]

Multimedia Appendix 5
Correlation matrix results.
[XLSX File (Microsoft Excel File), 16 KB - neuro_v3i1e50538_app5.xlsx]

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Abbreviations

ABI: acquired brain injury
HMD: head-mounted display
NIHSS: National Institute of Health Stroke Score
SSQ: Simulator Sickness Questionnaire
TBI: traumatic brain injury
TFQ: Technology Familiarity Questionnaire
TSI: time since injury
UQ: Usability Questionnaire
VR: virtual reality

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Review

Direct Clinical Applications of Natural Language Processing in Common Neurological Disorders: Scoping Review

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Abstract

Background: Natural language processing (NLP), a branch of artificial intelligence that analyzes unstructured language, is being increasingly used in health care. However, the extent to which NLP has been formally studied in neurological disorders remains unclear.

Objective: We sought to characterize studies that applied NLP to the diagnosis, prediction, or treatment of common neurological disorders.

Methods: This review followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) standards. The search was conducted using MEDLINE and Embase on May 11, 2022. Studies of NLP use in migraine, Parkinson disease, Alzheimer disease, stroke and transient ischemic attack, epilepsy, or multiple sclerosis were included. We excluded conference abstracts, review papers, as well as studies involving heterogeneous clinical populations or indirect clinical uses of NLP. Study characteristics were extracted and analyzed using descriptive statistics. We did not aggregate measurements of performance in our review due to the high variability in study outcomes, which is the main limitation of the study.

Results: In total, 916 studies were identified, of which 41 (4.5%) met all eligibility criteria and were included in the final review. Of the 41 included studies, the most frequently represented disorders were stroke and transient ischemic attack (n=20, 49%), followed by epilepsy (n=10, 24%), Alzheimer disease (n=6, 15%), and multiple sclerosis (n=5, 12%). We found no studies of NLP use in migraine or Parkinson disease that met our eligibility criteria. The main objective of NLP was diagnosis (n=20, 49%), followed by disease phenotyping (n=17, 41%), prognostication (n=9, 22%), and treatment (n=4, 10%). In total, 18 (44%) studies used only machine learning approaches, 6 (15%) used only rule-based methods, and 17 (41%) used both.

Conclusions: We found that NLP was most commonly applied for diagnosis, implying a potential role for NLP in augmenting diagnostic accuracy in settings with limited access to neurological expertise. We also found several gaps in neurological NLP research, with few to no studies addressing certain disorders, which may suggest additional areas of inquiry.

Trial Registration: Prospective Register of Systematic Reviews (PROSPERO) CRD42021228703; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=228703

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KEYWORDS

natural language processing; NLP; unstructured; text; machine learning; deep learning; neurology; headache disorders; migraine; Parkinson disease; cerebrovascular disease; stroke; transient ischemic attack; epilepsy; multiple sclerosis; cardiovascular; artificial intelligence; Parkinson; neurological; neurological disorder; scoping review; diagnosis; treatment; prediction

Introduction

The implementation of the electronic medical record (EMR) in health care systems has resulted in a remarkable increase in the amount of digital patient data [1], much of which is text-based and stored in an unstructured, narrative format [2-4]. While unstructured text is a rich data source, analyses of these data often require time- and cost-intensive manual processing [3]. Natural language processing (NLP), a type of artificial intelligence that automatically derives meaning from unstructured language, can significantly reduce costs and enhance the quality of health care systems by converting unstructured text into a structured form that can be processed by computers [2,4,5].

Approaches to NLP can use rule-based techniques, machine learning (ML), or a combination of both [6-8]. Between the fifth and eighth decades of the 20th century, NLP approaches were predominantly rule-based, using a set of rules defined by human experts [7,9] to systematically extract meaning from unstructured text. Rule-based methods are comprehensible by humans but difficult to generalize [7,9]. Driven by recent advances in computing power and access to computing resources, contemporary approaches to NLP have increasingly incorporated ML, which possesses greater scalability [7] than rule-based methods despite the need for greater computational power to construct ML-based NLP models. Most recently, complex ML methods such as deep learning (DL), which are based on neural networks and larger datasets than conventional ML approaches, have become popular approaches to address NLP tasks [9,10].

The high prevalence of unstructured text in EMR systems creates an ideal use case for NLP in health care. However, the majority of current NLP research remains focused on nonneurological conditions such as mental health, cancer, and pneumonia [5]. The dearth of neurological NLP research is out of proportion to the worldwide importance of neurological conditions, both in terms of public health burden and cost. For instance, cerebrovascular disease occupies the second leading cause of death worldwide [11], and in the United States, neurological and musculoskeletal disorders generate the greatest number of years lost to disability [12]. Finally, the estimated annual cost of the most prevalent neurological diseases in the United States is nearly US $800 billion [12].

Neurology is a specialty that is uniquely well suited to benefit from NLP approaches. The data used in the diagnosis and management of neurological conditions, such as examination findings or clinical impressions, are often recorded as narrative, unstructured text in clinical documentation. Aside from clinical notes containing the patient history and neurological examination, reports from radiology [13,14], sonography, or electrophysiology studies are integral to neurological practice and often are crucial for detection, prognosis, and treatment. Further, NLP analysis of spoken language may allow the detection of certain neurodegenerative conditions such as Alzheimer disease in their early stages [15]. Given the unique position of neurology with respect to NLP and the relative lack of research on the applications of NLP in neurology, we sought to conduct a scoping review in order to quantify and characterize studies that directly applied NLP for clinical use in common neurological disorders.

Methods

Literature Search Strategy and Eligibility Criteria

This review was conducted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines (Multimedia Appendix 1) and was registered with the Prospective Register of Systematic Reviews (PROSPERO CRD42021228703). Our search was conducted using Ovid Embase and MEDLINE on May 11, 2022 (Multimedia Appendix 2 [16-22]). Based on the most globally prevalent and costly neurological disorders [11], studies investigating the use of NLP in Alzheimer disease (exclusive of Alzheimer disease–related disorders), Parkinson disease, stroke and transient ischemic attack, epilepsy, multiple sclerosis (MS), and migraine were included.

Studies that used NLP to analyze radiographic findings without any clinical correlation (eg, silent brain infarcts) or for purposes other than diagnosis, detection, phenotyping, subtyping, prognostication, risk stratification, or therapy were excluded. We excluded studies with populations comprised of patients with heterogeneous diseases or ambiguously defined populations (eg, we excluded studies that used a patient cohort consisting of patients with both Alzheimer dementia and mild cognitive impairment) as well as studies that did not use NLP for direct clinical applications. Examples of indirect clinical applications include the use of NLP to identify cohorts for subsequent model development or conduct epidemiological associations between cohorts without direct impact on clinical practice. We additionally excluded abstracts, conference proceedings, reviews, and editorials.

Data Extraction

A medical librarian (SW) with expertise in scoping reviews first conducted a literature search (Multimedia Appendix 2) based on our eligibility criteria to generate a list of abstracts, which were then imported into a web application (Covidence Ltd) for initial screening by 3 authors (BRK, LJB, and IL). After the abstract screening was completed, full-text papers for screened abstracts were reviewed by 2 authors (BRK and IL) to determine eligibility for inclusion. Disagreements at both stages were resolved by discussion and consensus.

Using the final list of full-text studies, study characteristics were manually extracted by 1 author (IL) and charted in a REDCap (Research Electronic Data Capture; REDCap Consortium) web

database form, which was subsequently reviewed by a second author (BRK) for accuracy. The data charting form was initially tested by the data extractor (IL) and revised after feedback from all coauthors (BRK, NJ, LJB, and SW). We extracted study publication year, population size, country of origin, journal field (eg, medical informatics, clinical neurology, nonclinical neuroscience, clinical medicine, or other), neurological disorder, and target of NLP (eg, diagnosis or detection, phenotyping or subtyping and severity, prognostication or risk stratification, or disease management or therapy). Each study could have multiple targets whenever applicable.

For each study, the source language to which NLP techniques were applied was also extracted. For studies conducted in or authored by teams from non-English–speaking countries, the source language was extrapolated directly as described from the study methodology. If the source language was a publicly available research dataset or ontology (eg, MetaMap ontology or ADReSS dataset, both of which use English), the source language was reported as English. Source of language for NLP (eg, clinical notes, radiographic reports, speech audio, or other) and type of study (eg, model derivation, validation, or both) were also noted. Validation studies were defined as studies that specifically investigated the validation of a derived model in a population external to the original model derivation population. Our definition of validation studies did not include validation on held-out test sets as part of model derivation. If the NLP model was both derived and externally validated in the same study, the population size included the additional population used for validation. Simulated patients, who were used as a training set in one study, were included in the population size. If no population size was mentioned in the studies, the number of text instances (eg, clinical notes and radiographic reports) was recorded.

We additionally extracted the study's NLP approaches (ie, rule-based methods, ML, or both). Rule-based NLP included any approaches that used keyword searches, pattern matching, regular expressions, or ontological systems for word-concept mapping, text preprocessing, or classification. ML-based NLP comprised both conventional ML and DL approaches and both were distinguished as dichotomous study characteristic variables but could co-occur in the studies. A study was characterized as including any of these methods if either ML or DL was used at any point in model development for the study.

Under the category of conventional ML methods, linear regression, logistic regression, support vector machines (SVMs), naïve Bayes classifiers, decision trees, random forest classifiers, k-nearest neighbor algorithms, gradient boosting techniques such as extreme gradient boosting, latent Dirichlet allocation, and shallow neural networks were included. Under the definition of shallow neural network, we included any approaches using Word2vec or other "-2vec" word-embedding techniques that use a neural network to construct word contexts and extract semantic and syntactic meaning from text [23,24]. We also included other types of regression, such as lasso regression, which is often used for dimensionality reduction, in the conventional ML category.

DL techniques included convolutional neural networks, recurrent neural networks (RNNs), long- and short-term memory networks, multilayer perceptrons, and transformers. Studies using long- and short-term memory networks were also categorized as using an RNN. We also note that neural networks of unspecified type and number of layers, which were not clearly referred to as DL in the study, were not included in this category.

Results

Included Studies

In total, 916 studies were identified from our search strategy, of which 271 were duplicates and were excluded. We then screened the resulting 645 abstracts, of which 565 were excluded due to not meeting initial eligibility criteria. Of the remaining 80 studies, 39 (49%) were excluded. The 2 most common reasons for exclusion were the use of NLP for nonclinical applications (n=15, 38%) and heterogeneous clinical populations (n=12, 31%). In total, 41 (4.5%) of the 916 studies from the original search results were ultimately included for review (Figure 1 and Table 1).

Of the 41 included studies, NLP was applied to stroke or transient ischemic attack in 20 (49%) studies, epilepsy in 10 (24%) studies, Alzheimer dementia in 6 (15%) studies, and MS in 5 (12%) studies. We found no studies applying NLP to Parkinson disease or migraine that met our eligibility criteria. Across all neurological conditions, NLP was most commonly applied for the purposes of detection or diagnosis (n=20, 49%), followed by clinical disease phenotyping or subtyping (n=17, 41%), prognostication or risk stratification (n=9, 22%), and management or therapy (n=4, 10%; Table 2).

Figure 1. Study PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram. NLP: natural language processing.

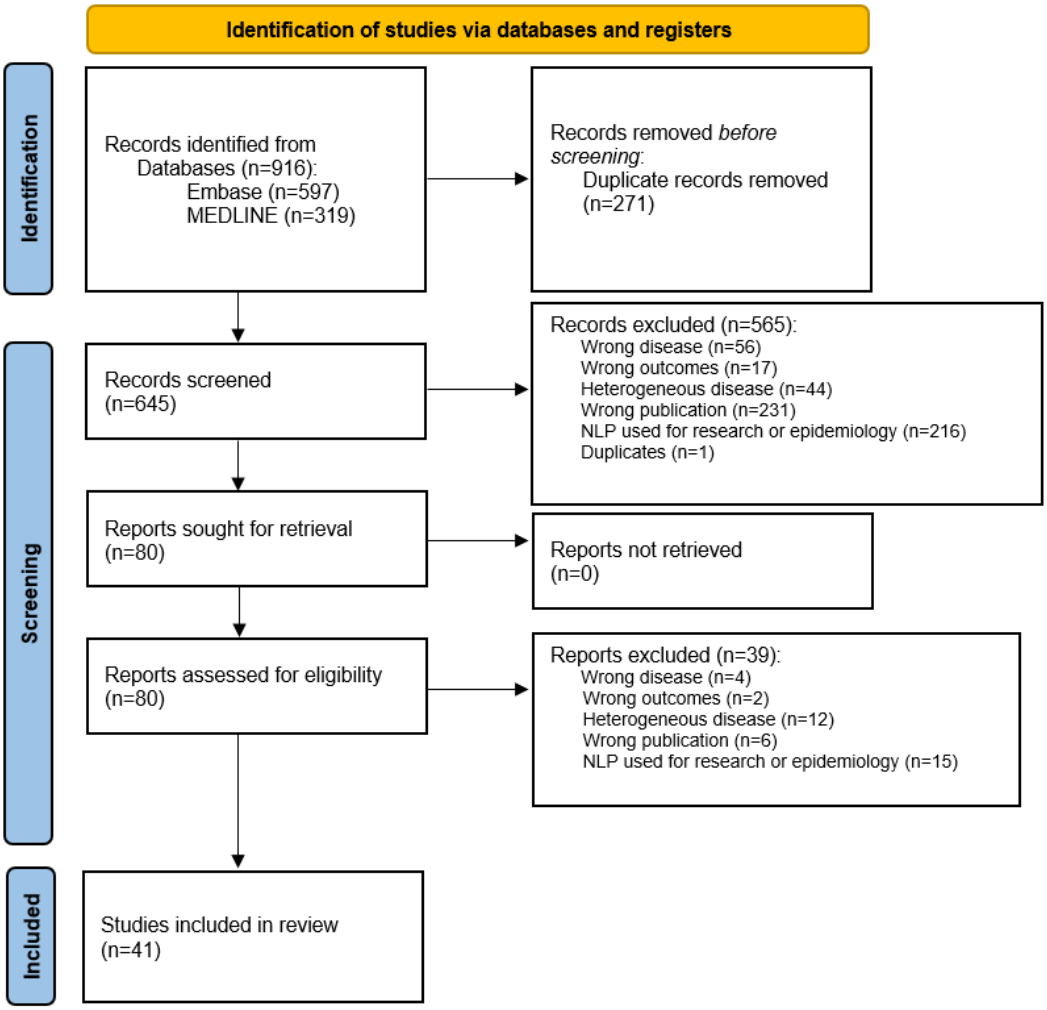


Table 1. Included studies.

Paper authors	Publication date	Country	Source text	Journal field	External model validation	Condition being studied	Purpose of NLP[a]	NLP method	Deep learning	Algorithms used	Study outcomes
Miller et al [19]	May 9, 2022	United States	Radiology reports	Clinical neurology	Yes	Stroke	Detection or diagnosis	Rule-based, ML[b]	Yes	Random forest, linear regression, KNN[c], lasso regression, MLP[d], transformer	Radiographic complications of ischemic stroke (eg, hemorrhagic transformation)
Lay et al [25]	October 23, 2020	Australia	Clinical notes	Clinical neurology	No	Epilepsy	Detection or diagnosis	ML	No	Latent Dirichlet allocation	Identifying themes in medical records in patients with PNES[e], congruency of themes
Mayampurath et al [26]	June 24, 2021	United States	Clinical notes	Clinical neurology	No	Stroke	Detection or diagnosis, clinical disease phenotyping or severity	ML	No	SVM[f], logistic regression	Acute stroke diagnosis, stroke severity and subtypes
Li et al [16]	March 1, 2021	United States	Radiology reports	Neuroradiology	Yes	Stroke	Detection or diagnosis	Rule-based, ML	No	Random forest	Acute or subacute ischemic stroke cases before and during COVID-19
Lineback et al [27]	July 13, 2021	United States	Clinical notes	Clinical neurology	No	Stroke	Prognosis or risk stratification	ML	No	SVM, naïve Bayes, random forest, logistic regression, shallow neural network, lasso regression, ensemble, boosting	30-day stroke readmission, 30-day all-cause readmission
Liu et al [28]	April 13, 2022	China	Speech	Public health	No	Alzheimer disease	Detection or diagnosis	ML	Yes	SVM, random forest, logistic regression, boosting, CNN[g], transformer	Detection of Alzheimer disease from speech
Mahajan and Baths [29]	February 5, 2021	India	Speech	Nonclinical neuroscience	No	Alzheimer disease	Detection or diagnosis	ML	Yes	CNN, RNN[h] (LSTM[i])	Detection of Alzheimer disease from speech
Bacchi et al [30]	February 20, 2022	Australia	Clinical notes	Clinical medicine	No	Stroke	Clinical disease phenotyping or severity	Rule-based, ML	No	Random forest, decision tree, logistic regression, neural network with an unspecified number of layers	Extraction of stroke key performance indicators
Hamid et al [31]	October 14, 2013	United States	Clinical notes	Clinical neurology	No	Epilepsy	Detection or diagnosis	Rule-based, ML	No	Naïve Bayes	Identification of patients with PNES
Yu et al [13]	September 16, 2020	Canada	Radiology reports	Medical informatics	No	Stroke	Detection or diagnosis, clinical disease phenotyping or severity	Rule-based	No	N/A[j]	Identification of the presence and location of vascular occlusions and other stroke-related attributes

Paper authors	Publication date	Country	Source text	Journal field	External model validation	Condition being studied	Purpose of NLP[a]	NLP method	Deep learning	Algorithms used	Study outcomes
Bacchi et al [32]	January 17, 2019	Australia	Clinical notes and radiology reports	Clinical neurology	No	Stroke	Detection or diagnosis	ML	Yes	Random forest, decision tree, CNN, RNN (LSTM)	Determining the cause of TIA[k]-like presentations (cerebrovascular vs noncerebrovascular)
Garg et al [33]	May 15, 2019	United States	Clinical notes and radiology reports	Clinical neurology	No	Stroke	Clinical disease phenotyping or severity	Rule-based, ML	No	SVM, random forest, logistic regression, KNN, boosting, ensemble (stacking logistic regression, extra trees classifier)	Ischemic stroke subtypes
Zhao et al [21]	March 8, 2021	United States	Clinical notes	Medical informatics	Yes	Stroke	Detection or diagnosis, clinical disease phenotyping or severity	Rule-based, ML	No	Random forest, logistic regression	Incidence of stroke, stroke subtypes
Pevy et al [34]	October 1, 2021	United Kingdom	Speech	Clinical neurology	No	Epilepsy	Detection or diagnosis	ML	No	Random forest	Distinguishing between PNES and epilepsy, hesitations and repetitions in descriptions of epileptic seizures versus PNES
Guan et al [35]	December 10, 2020	United States	Echocardiographic reports	Clinical neurology	No	Stroke	Clinical disease phenotyping or severity	Rule-based, ML	No	SVM, random forest, decision tree, logistic regression, KNN	Subtyping and phenotyping cardioembolic stroke
Cui et al [36]	June 26, 2014	United States	Clinical notes	Medical informatics	No	Epilepsy	Clinical disease phenotyping or severity	Rule-based	No	N/A	Epilepsy phenotype extraction with correlated anatomic location
Heo et al [37]	December 16, 2020	South Korea	Radiology reports	Clinical medicine	No	Stroke	Prognosis or risk stratification	ML	Yes	SVM, random forest, decision tree, shallow neural network, lasso regression, CNN, RNN (LSTM), MLP	Prediction of poor stroke outcome
Zanotto et al [38]	November 1, 2021	Brazil	Clinical notes	Medical informatics	No	Stroke	Prognosis or risk stratification, clinical disease phenotyping or severity	Rule-based, ML	Yes	SVM, naïve Bayes, random forest, KNN, CNN, transformer	Prediction of stroke outcome measurements and extraction of patient characteristics
Barbour et al [17]	May 21, 2019	United States	Clinical notes	Clinical neurology	Yes	Epilepsy	Prognosis or risk stratification	Rule-based	No	N/A	Risk factors for SUDEP[l]

Paper authors	Publication date	Country	Source text	Journal field	External model validation	Condition being studied	Purpose of NLP[a]	NLP method	Deep learning	Algorithms used	Study outcomes
Kim et al [39]	February 28, 2019	United States	Radiology reports	Nonclinical neuroscience	No	Stroke	Detection or diagnosis	ML	No	SVM, naïve Bayes, decision tree, logistic regression	Identification of acute ischemic stroke, features of acute ischemic stroke reports versus nonischemic stroke reports
Davis et al [40]	October 22, 2013	United States	Clinical notes, letters, and problem lists	Medical informatics	No	MS[m]	Clinical disease phenotyping or severity	Rule-based	No	N/A	Extraction of clinical traits of patients with MS
Glauser et al [41]	January 22, 2020	United States	Speech	Clinical neurology	No	Epilepsy	Detection or diagnosis	Rule-based, ML	No	SVM	Epilepsy psychiatric comorbidities
Cohen et al [42]	May 22, 2016	United States	Clinical notes	Medical informatics	No	Epilepsy	Prognosis or risk stratification, management or therapy	ML	No	SVM, naïve Bayes	Identification of potential candidates for surgical intervention for pediatric drug–resistant epilepsy, performance of classification algorithm over time
Alim-Marvasti et al [43]	February 10, 2021	United Kingdom	Clinical notes and radiology reports	Medical informatics	No	Epilepsy	Clinical disease phenotyping or severity, prognosis or risk stratification	Rule-based, ML	No	SVM, naïve Bayes, random forest, logistic regression, boosting	Localizing the epileptogenic zone (temporal vs extratemporal), postsurgical prognosis and outcome
Balagopalan et al [44]	April 27, 2021	Canada	Speech	Nonclinical neuroscience	No	Alzheimer disease	Detection or diagnosis	ML	Yes	SVM, naïve Bayes, random forest, linear regression, shallow neural network, ridge regression, transformer	Detection of Alzheimer disease from speech, prediction of MMSE[n]
Martinc et al [45]	June 14, 2021	Slovenia	Speech	Nonclinical neuroscience	No	Alzheimer disease	Detection or diagnosis	ML	Yes	SVM, random forest, logistic regression, boosting, transformer	Detection of Alzheimer disease from speech
Liu et al [46]	April 5, 2022	United States	Speech	Clinical neurology	No	Alzheimer disease	Detection or diagnosis	ML	Yes	Shallow neural network, transformer	Detection of Alzheimer disease from speech
Nelson et al [47]	December 22, 2016	United States	Clinical notes	Pharmacy	No	MS	Clinical disease phenotyping or severity	Rule-based	No	N/A	Identification of MS phenotype, percentages of each phenotype
Deng et al [18]	April 8, 2022	China	Clinical notes and radiology reports	Nonclinical neuroscience	Yes	Stroke	Management or therapy	Rule-based, ML	Yes	Transformer	Performance of system to generate ICH[o] treatment plan

Paper authors	Publication date	Country	Source text	Journal field	External model validation	Condition being studied	Purpose of NLP[a]	NLP method	Deep learning	Algorithms used	Study outcomes
Chase et al [48]	February 28, 2017	United States	Clinical notes	Medical informatics	No	MS	Detection or diagnosis	Rule-based, ML	No	Naïve Bayes	Early detection of MS
Wissel et al [49]	November 29, 2019	United States	Clinical notes	Clinical neurology	No	Epilepsy	Prognosis or risk stratification, management or therapy	ML	No	SVM	Epilepsy surgery candidacy score
Sung et al [50]	February 28, 2020	Taiwan	Clinical notes	Medical informatics	No	Stroke	Clinical disease phenotyping or severity	Rule-based, ML	No	SVM, random forest, decision tree, logistic regression, KNN, ensemble	Classification of ischemic stroke subtypes
Sung et al [20]	November 19, 2021	Taiwan	Clinical notes and radiology reports	Clinical neurology	Yes	Stroke	Prognosis or risk stratification	ML	Yes	Random forest, logistic regression, transformer	Prediction of poor functional outcome after acute ischemic stroke
Yang et al [51]	October 20, 2020	Canada	Clinical notes	Medical informatics	No	MS	Clinical disease phenotyping or severity	Rule-based ML	Yes	Shallow neural network, CNN, RNN	Expanded disability status scale score, expanded disability status scale subscore
Xie et al [52]	February 22, 2022	United States	Clinical notes	Medical informatics	No	Epilepsy	Clinical disease phenotyping or severity	ML	Yes	Transformer	Seizure freedom, seizure frequency, date of last seizure
Sung et al [53]	February 8, 2018	Taiwan	Clinical notes	Medical informatics	No	Stroke	Management or therapy	Rule-based	No	N/A	Performance of EMR[p] interface that determines eligibility for intravenous thrombolytic therapy
Sung et al [54]	February 17, 2022	Taiwan	Clinical notes and radiology reports	Medical informatics	No	Stroke	Prognosis or risk stratification	Rule-based, ML	No	Logistic regression, boosting, unspecified penalized logistic regression method, ensemble (extra trees classifier)	Prediction of poor functional outcome after acute ischemic stroke
Xia et al [55]	November 11, 2013	United States	Clinical notes and radiology reports	Nonclinical neuroscience	No	MS	Detection or diagnosis, clinical disease phenotyping or severity	Rule-based, ML	No	Lasso regression, stepwise regression	Identification of patients with MS, severity of MS
Ong et al [22]	June 19, 2020	United States	Radiology reports	Nonclinical neuroscience	Yes	Stroke	Detection or diagnosis, clinical disease phenotyping or severity	ML	Yes	Random forest, decision tree, logistic regression, KNN, RNN (LSTM)	Ischemic stroke presence, location, and acuity

Paper authors	Publication date	Country	Source text	Journal field	External model validation	Condition being studied	Purpose of NLP[a]	NLP method	Deep learning	Algorithms used	Study outcomes
Roshanzamir et al [56]	March 9, 2021	Iran	Speech	Medical informatics	No	Alzheimer disease	Detection or diagnosis	ML	Yes	Logistic regression, shallow neural network, CNN, RNN (LSTM) transformer	Detection of Alzheimer disease from speech
Rannikmäe et al [57]	June 15, 2021	United Kingdom	Radiology reports	Medical informatics	No	Stroke	Clinical disease phenotyping or severity	Rule-based, ML	Yes	RNN	Stroke subtypes

[a]NLP: natural language processing.
[b]ML: machine learning.
[c]KNN: k-nearest neighbor.
[d]MLP: multilayer perceptron.
[e]PNES: psychogenic nonepileptic seizures.
[f]SVM: support vector machine.
[g]CNN: convolutional neural network.
[h]RNN: recurrent neural network.
[i]LSTM: long- and short-term memory network.
[j]N/A: Not applicable.
[k]TIA: transient ischemic attack.
[l]SUDEP: sudden unexpected death in epilepsy.
[m]MS: multiple sclerosis.
[n]MMSE: Mini-Mental Status Examination.
[o]ICH: intracerebral hemorrhage.
[p]EMR: electronic medical record.

Table 2. Overall study characteristics: journal field, target of NLP[a], and neurological condition.

Study characteristics	Studies (n=41), n (%)
Condition	
Stroke	20 (49)
Epilepsy	10 (24)
Alzheimer disease	6 (15)
Multiple sclerosis	5 (12)
Target of NLP	
Diagnosis	20 (49)
Phenotyping	17 (42)
Prognosis	9 (22)
Therapy	4 (10)
Journal field	
Medical informatics	15 (37)
Clinical neurology	14 (34)
Nonclinical neuroscience	7 (17)
Clinical medicine	2 (5)
Other[b]	3 (7)

[a]NLP: natural language processing.
[b]Other includes studies published in pharmacy, public health, and neuroradiology journals.

Of the 41 studies, the language sources for NLP comprised clinical notes (n=25, 61%); radiology reports (n=14, 34%); speech (n=8, 20%); and other sources (n=2, 5%) that included echocardiography reports, letters to referring providers, and problem lists (Table 3). Of studies with speech as the language source, half (4/8, 50%) analyzed transcripts only, whereas half additionally incorporated acoustic features from the audio files themselves. These transcripts and audio files were largely from research datasets (eg, ADReSS and Pitt corpus). Two studies analyzed transcripts from interviews with patients. In the study including problem lists, it is unknown who reported the problems.

Table 3. Overall study characteristics: NLP[a] methods and language sources.

Study characteristics	Studies (n=41), n (%)
NLP method	
Rule-based	23 (56)
Machine learning	35 (85)
Type of machine learning	
Conventional machine learning	31 (76)
Deep learning	16 (39)
Source text	
Clinical notes	25 (61)
Radiology reports	14 (34)
Speech	8 (20)
Other[b]	2 (5)

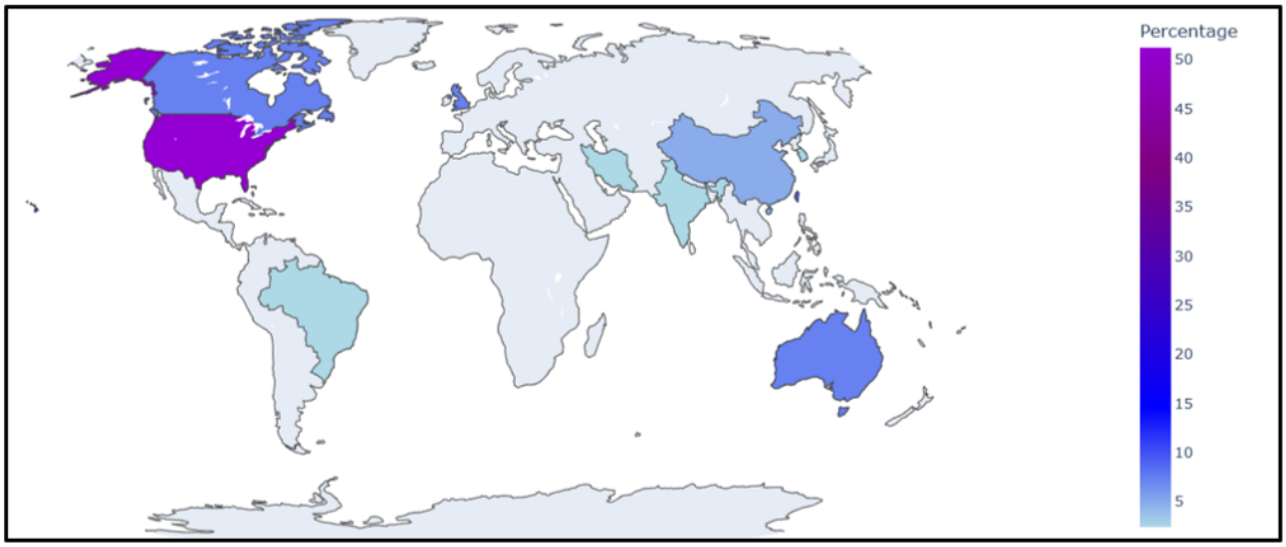
[a]NLP: natural language processing.

[b]Other includes echocardiography reports, problem lists, and letters to referring providers.

Of the 41 studies, the most common source language for NLP was English (n=39, 95%), Portuguese in 1 (2%) study, and unspecified in the remaining 1 study (which was of Chinese nationality, not multicentric). When patient population size was recorded, the median was 1091 (IQR 188-4211). In studies that did not specify a population size (n=4, 10%), the median number of clinical or radiographic notes was 2172 (IQR 1155.5-22,018.0).

Papers were most commonly published in medical informatics (n=15, 37%) journals, followed closely by clinical neurology (n=14, 34%) journals. Seven (17%) studies were published in nonclinical neuroscience journals; 2 (5%) in clinical medicine journals; and 1 (2%) each in neuroradiology, public health, and pharmacy journals. Studies were mostly conducted in the United States (n=21, 51%), followed by Taiwan (n=4, 10%) and the United Kingdom, Canada, and Australia (n=3, 7% each). Two (5%) studies were conducted in China, and 1 (2%) study was conducted in each of South Korea, Brazil, Iran, India, and Slovenia (Figure 2).

Figure 2. Proportion of included studies (n=41), organized according to country of origin: the United States (n=21, 51%); Taiwan (n=4, 10%); the United Kingdom, Canada, and Australia (n=3, 7% each); China (n=2, 5%); and South Korea, Brazil, Iran, India, and Slovenia (n=1, 2% each).



Only 6 (15%) studies used strictly rule-based methods. The majority of studies incorporated ML (n=35, 85%), either exclusively (n=18, 44%) or in combination with rule-based methods (n=17, 41%). Of the studies that used ML, most (n=31, 89%) used conventional ML methods, whereas 16 (46%) used DL approaches (Table 3), and 12 (34%) used a combination of both conventional ML and DL approaches.

As shown in Figure 3, the most frequently used conventional ML algorithms were random forest (n=18, 58%), SVM (n=15, 48%), and logistic regression (n=15, 48%) models. Among studies using DL approaches, transformers (n=10, 63%) were the most commonly used algorithm, followed by convolutional neural networks and RNNs (each n=7, 44%). The co-occurrence of random forest and transformer algorithms was a prevalent trend in research combining traditional ML with DL methodologies (n=6, 15%). Studies that used DL only began to appear in 2019 and later (Figure 4). The most often reported performance metrics for ML models were precision or recall (n=31, 76%), accuracy (n=22, 54%), area under the receiver operating curve (n=20, 49%), and F_1-score (n=19, 46%).

Figure 3. Relative proportions of machine learning algorithms used by the included NLP models. CNN: convolutional neural network; KNN: k-nearest neighbor; LSTM: long- and short-term memory networks; MLP: multilayer perceptron; RNN: recurrent neural network; SVM: support vector machine. *Other includes stepwise regression, ridge regression, an unspecified penalized regression method, latent Dirichlet allocation, and an unspecified neural network with an unspecified number of layers.

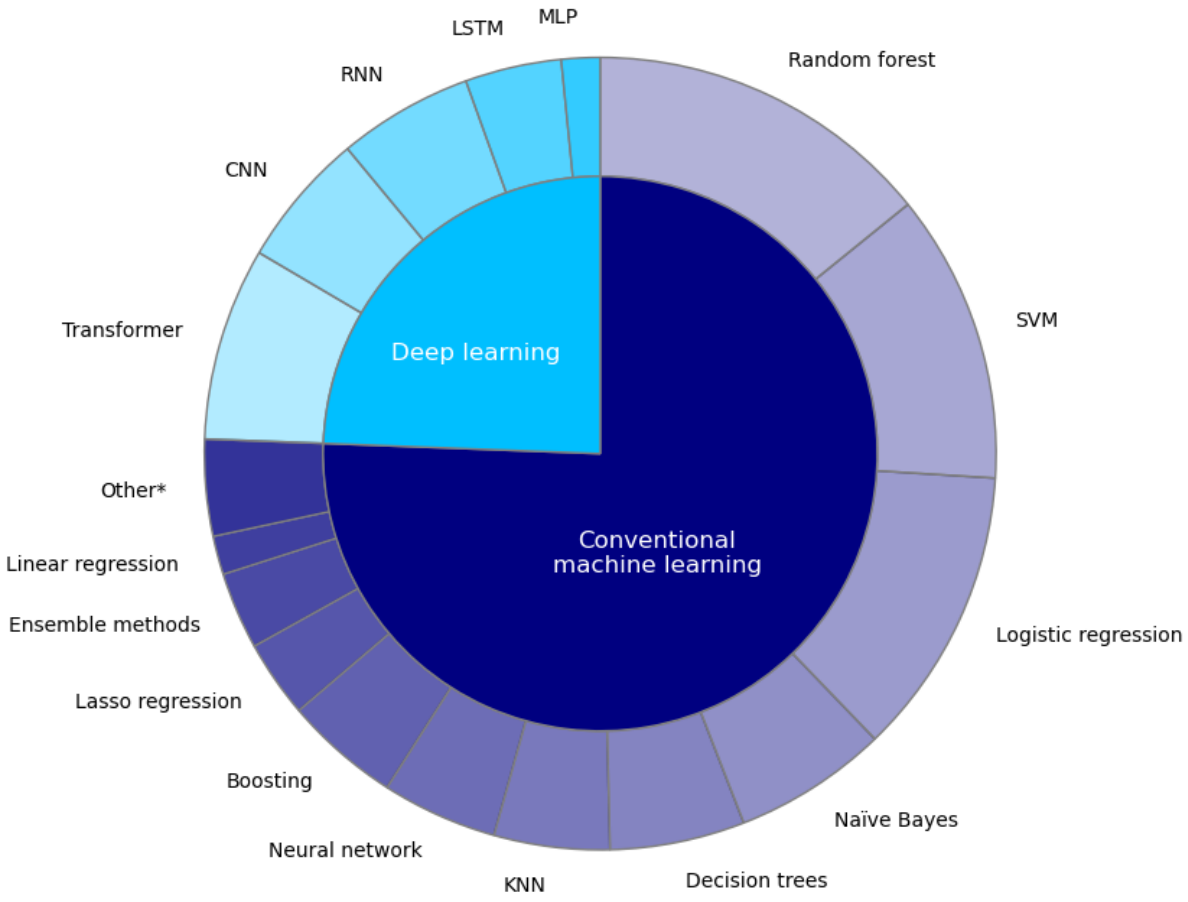
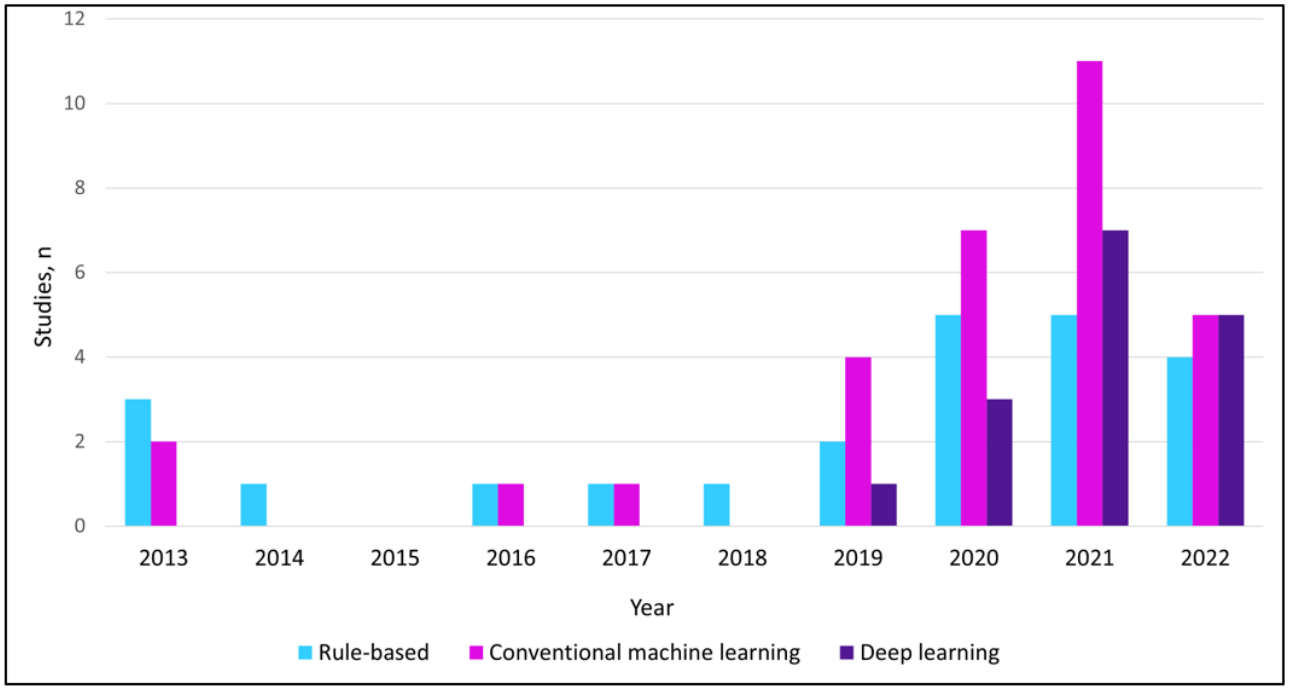


Figure 4. Number of studies applying natural language processing (NLP) to neurological conditions, stratified by NLP methodology and publication year.



All 41 studies were model derivation studies, with only 7 (17%) studies conducting additional external validation (Multimedia Appendix 2). Furthermore, nearly all the study models were developed retrospectively and were not applied in practice or deployed in real-world environments, except for 3 studies. A study by Li et al [16] developed a model for stroke detection from imaging reports and then applied it to quantify the change in stroke cases before and during the COVID-19 pandemic. A second by Sung et al [53], also in the stroke category, evaluated the deployment of a user-interface system to determine intravenous thrombolysis eligibility built on the NLP model devised. A third study by Wissel et al [49] created a model to identify surgical resection candidates in adult patients with epilepsy. The model was retrained prospectively to incorporate new information.

Study Characteristics, Stratified by Condition

In studies focused on Alzheimer dementia, diagnosis and detection was the only target of NLP (6/6, 100%). Disease phenotyping and subtyping was the most common purpose of NLP in stroke (10/20, 50%) and MS (4/5, 80%), whereas prognostication was seen as often as diagnosis in epilepsy studies (4/10, 40%; Figure S9 in Multimedia Appendix 2). Studies that applied NLP for the purpose of disease treatment or management were limited to stroke and epilepsy (Figure S9 in Multimedia Appendix 2).

Rule-based methods were used across all studies, except for Alzheimer dementia, in which only ML approaches were used (Figure S10 in Multimedia Appendix 2). Conventional ML methods were used most often by Alzheimer dementia studies (5/6, 83%), followed by stroke (16/20, 80%). Similarly, DL methods were used predominantly by Alzheimer dementia (6/6, 100%) and stroke (8/20, 40%) studies (Figure S10 in Multimedia Appendix 2). The transformer was the DL method used most frequently in Alzheimer disease-related studies (5/6, 83%).

Discussion

Principal Findings

In this scoping review, 41 studies [13,16-22,25-57] that investigated direct clinical applications of NLP to common neurological disorders were identified. We found that the majority of these studies focused on detection and diagnosis and applied NLP to stroke, whereas we found no studies of NLP that met our eligibility criteria in the clinical areas of migraine or Parkinson disease. Methodologically, ML techniques were used more often than rule-based methods, but a considerable number of studies still relied on rule-based approaches in combination with ML. While we observed that DL began to emerge as a methodology for NLP in 2019, we found that the transformer was the most commonly used DL algorithm overall.

At the time of writing, we believe our scoping review to be the first to examine direct clinical NLP applications in common neurological conditions. One prior review [58] investigated NLP applications across the combined clinical specialties of neurosurgery, spine surgery, and neurology, whereas another evaluated the use of NLP in both psychiatry and clinical neuroscience [59]. However, neither reviews analyzed studies and NLP applications according to neurological condition. More importantly, these reviews included many studies where NLP was not applied for direct clinical use, instead aiming to perform tasks such as characterizing patient cohorts [58], analyzing information extraction, or determining causal inference between concepts [59]. In contrast to this prior work, our review focused on direct clinical applications of NLP.

Of note, we found no studies applying NLP to migraine or Parkinson disease that met our eligibility criteria, thereby highlighting a potential gap in NLP research focusing on these disorders. This is perhaps unexpected, as the combined

prevalence of migraine and Parkinson disease in the United States exceeds that of both stroke and MS [12]. Two explanations may account for this finding. One is that migraine and Parkinson disease may rely less on radiographic imaging studies and their reports to establish a diagnosis than stroke, Alzheimer dementia, or MS. Given that many ML applications in stroke have focused on neuroimaging [60], it is plausible that stroke imaging reports could represent an important source of data for NLP analyses. Indeed, the results of our review demonstrate that stroke-related NLP studies made use of radiographic reports as often as clinical notes for source text, which could have resulted in a relatively higher number of NLP studies within stroke than in other neurological conditions.

A second explanation may be that Alzheimer disease is a more common cause of dementia worldwide than dementing syndromes associated with Parkinson disease [61] and has in turn garnered a larger proportion of research funding. National Institutes of Health [62] research funding for Alzheimer dementia was approximately US $3 billion in 2022, as compared to US $259 million for Parkinson disease.

Our finding that NLP was most frequently applied to diagnostic problems is expected, given that clinical decision support is a common focus of artificial intelligence in medicine [63]. Historically, clinical decision support has also played an important role in medical informatics by constituting the main focus of archetypal systems such as MYCIN, INTERNIST-1, and DXplain, which were first developed in the 1970s and 1980s [64]. An alternative explanation is that the shortage of neurologists that already exists worldwide [65] may have potentially created a more urgent need for detection-oriented NLP applications rather than NLP applications targeting therapeutic management or prognostication.

Though diagnosis was the most common target of NLP overall, we found that epilepsy-related studies focused as much on prognostication as they did on diagnostic tasks. Given that roughly one-third of all patients with epilepsy are drug resistant [66], determining good surgical resection candidates as well as predicting surgical outcomes are important objectives that have been the focus of considerable research [67]. Consistent with this, the epilepsy-related studies in the prognostication category were directed toward identifying adult [49] and pediatric [42] surgical candidates, predicting postsurgical outcomes [43], and detecting risk factors for sudden unexpected death in epilepsy [17].

With respect to the types of ML models we found in our review, the relatively high proportion of conventional ML-based studies using random forest and SVM (18/31, 58% and 15/31, 48%, respectively) may have been related to the fact that SVM together with random forest models generally represented the dominant ML techniques prior to the advent of neural networks [68] in diagnostic and clinical decision support applications [63,69,70]. Despite its position as a potentially more basic classification method than either SVM or random forest, logistic regression was used as commonly as SVM in our analysis.

Furthermore, while we found that SVM and random forest models were common in ML-based NLP approaches, the optimal problems these models address are fundamentally different. SVM generally works best as a binary classifier, whereas random forest models are best used for classification tasks involving multiple categories [71]. We found that the most frequently used ML algorithms in stroke-related NLP studies were random forest models. This matches the most frequent target of NLP in stroke-related studies, which was disease subtyping (a multiple classification problem).

Among DL algorithms, which are becoming increasingly widespread in NLP [72], the transformer was the most commonly used technique we identified. Unlike other word embedding methods, a transformer processes a whole sequence of text while preserving the context and meaning of words [59,73]. Another significant advantage of transformers is that they can use transfer learning, which first trains a model on a learning task and then applies the model to a separate but closely related task [58,74]. A prevalent example of transfer learning in our results is Bidirectional Encoder Representations From Transformers (BERT), a transformer model that was originally trained using publicly available text from Wikipedia and BookCorpus, a collection of free, unpublished novels consisting of over 50 million sentences [75,76]. BERT can then be further refined on a target training task and dataset before being passed to a separate classification algorithm [28]. This is helpful in situations where the target training set is small [28]. The high frequency of Alzheimer disease–related NLP studies we found using BERT is expected within this context, as these studies often used the ADReSS speech dataset that consists of only 78 healthy controls and 78 patients with Alzheimer disease [28,45].

A particularly important finding of our review is that although many of the NLP studies leveraged powerful and sophisticated computational tools, most studies constitute research work rather than reports of operationalization or evaluation in practical settings. This is consistent with the current state of clinical NLP outside of neurology, wherein real-world deployment of NLP models continues to be limited [7,77,78].

One major obstacle to the implementation of NLP in clinical practice is model generalizability [7]. Published NLP models are usually internally validated rather than externally validated [7,17], limiting the understanding of model accuracy beyond the model's original training environment [60]. We found this to be true for the majority of studies identified in our review. The lack of EMR standardization, including note formatting [17,78], documentation styles, and radiographic report structures across different medical institutions [7] and between clinicians, may partly account for our observations. Furthermore, the preponderance of English language as source text in NLP [79], as demonstrated by the single study in our review using non-English (Portuguese) text for analysis, suggests that the generalizability of NLP within neurology is most likely limited outside the English language.

Another major obstacle impeding the adoption of NLP tools is the inherent lack of transparency of ML-based algorithms [60], particularly artificial neural networks and other forms of DL approaches [80]. These approaches have low transparency because the computational methods they use to characterize relationships between inputs and outputs are not readily

intelligible to humans [7,78,80] acting as a black box that could undermine clinicians' trust in their performance.

The lack of well-defined regulatory guidelines and standards overseeing the artificial intelligence space [81] has furthered this mistrust. Compromise of personal health data, algorithmic bias, and the question of how to attribute culpability when diagnostic errors arise [82,83] are all ethical concerns that may serve to explain the relative paucity of studies across all neurological conditions that externally validated DL models.

Finally, the lack of portability of NLP applications into external EMRs is another factor that has restricted the development of NLP models to the research arena. External software modules containing ML and DL models are challenging to integrate into EMRs [1,84], as most implementations require a high level of computing infrastructure and technical expertise that many hospital information technology systems and personnel may lack [84]. Recent work suggests few EMR-integrated aggregative tools exist to display NLP findings to clinicians in a digestible format [85]. To address these barriers, some authors have advocated for collaborations between NLP researchers and EMR companies [77].

Limitations and Future Work

Our scoping review has several limitations. First, we note that the target of NLP was categorized according to author experience and interpretation of the literature, which may have underreported the application of the published NLP algorithms. Second, due to the variable performance metrics and outcomes across studies, we did not aggregate measurements of performance in our review, and we therefore could not reliably provide summary performance metrics for NLP models within individual diseases, applications, or outcomes. Future work should focus on individual outcomes within a clinical disorder for a more exact appraisal of NLP model performance than this review.

Third, this review only included studies based on common neurological disorders, direct clinical applications of NLP, and homogeneous clinical populations, which limited the number of studies we identified. It is therefore important to note that this review cannot be used to make definitive conclusions on the state of NLP research across all neurological disorders. Future efforts can be directed at characterizing the use of NLP across less common neurological disorders as well as in heterogeneous or ambiguously defined clinical populations. As NLP technologies continue to advance, it will also be critically important to evaluate studies that use newer transformers, such as GPT3, which have better performance than BERT models [59].

Conclusions

The abundance of unstructured text data in modern-day EMRs as well as the emphasis in neurology on narrative history and physical examination and heavy reliance on ancillary information such as radiographic reports and speech, all create an optimal use case for applying NLP for the diagnosis, management, or prognostication of neurological disorders. To our knowledge, this is the first attempt to systematically characterize research efforts to investigate direct NLP applications to common neurological conditions. Our review reveals gaps in neurological NLP research, showing a relative deficiency of NLP studies in subspecialties outside of stroke or epilepsy, and underlines the need to actualize NLP models outside of the research phase. Moreover, the current emphasis of NLP on diagnostic tasks suggests that NLP may be particularly useful in settings that lack access to neurological expertise.

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None.

Conflicts of Interest

NJ receives an honorarium for her work as an associate editor of Epilepsia. There are no other conflicts of interest to report.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews): checklist and explanation.
[PDF File (Adobe PDF File), 546 KB - neuro_v3i1e51822_app1.pdf]

Multimedia Appendix 2
Search strategy and additional data.
[DOCX File , 756 KB - neuro_v3i1e51822_app2.docx]

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Abbreviations

BERT: Bidirectional Encoder Representations From Transformers
DL: deep learning
EMR: electronic medical record
ML: machine learning
MS: multiple sclerosis
NLP: natural language processing

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PROSPERO: Prospective Register of Systematic Reviews
REDCap: Research Electronic Data Capture
RNN: recurrent neural network
SVM: support vector machine

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Original Paper

Smartphone Pupillometry and Machine Learning for Detection of Acute Mild Traumatic Brain Injury: Cohort Study

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Abstract

Background: Quantitative pupillometry is used in mild traumatic brain injury (mTBI) with changes in pupil reactivity noted after blast injury, chronic mTBI, and sports-related concussion.

Objective: We evaluated the diagnostic capabilities of a smartphone-based digital pupillometer to differentiate patients with mTBI in the emergency department from controls.

Methods: Adult patients diagnosed with acute mTBI with normal neuroimaging were evaluated in an emergency department within 36 hours of injury (control group: healthy adults). The PupilScreen smartphone pupillometer was used to measure the pupillary light reflex (PLR), and quantitative curve morphological parameters of the PLR were compared between mTBI and healthy controls. To address the class imbalance in our sample, a synthetic minority oversampling technique was applied. All possible combinations of PLR parameters produced by the smartphone pupillometer were then applied as features to 4 binary classification machine learning algorithms: random forest, k-nearest neighbors, support vector machine, and logistic regression. A 10-fold cross-validation technique stratified by cohort was used to produce accuracy, sensitivity, specificity, area under the curve, and F_1-score metrics for the classification of mTBI versus healthy participants.

Results: Of 12 patients with acute mTBI, 33% (4/12) were female (mean age 54.1, SD 22.2 years), and 58% (7/12) were White with a median Glasgow Coma Scale (GCS) of 15. Of the 132 healthy patients, 67% (88/132) were female, with a mean age of 36 (SD 10.2) years and 64% (84/132) were White with a median GCS of 15. Significant differences were observed in PLR recordings between healthy controls and patients with acute mTBI in the PLR parameters, that are (1) percent change (mean 34%, SD 8.3% vs mean 26%, SD 7.9%; P<.001), (2) minimum pupillary diameter (mean 34.8, SD 6.1 pixels vs mean 29.7, SD 6.1 pixels; P=.004), (3) maximum pupillary diameter (mean 53.6, SD 12.4 pixels vs mean 40.9, SD 11.9 pixels; P<.001), and (4) mean constriction velocity (mean 11.5, SD 5.0 pixels/second vs mean 6.8, SD 3.0 pixels/second; P<.001) between cohorts. After the synthetic minority oversampling technique, both cohorts had a sample size of 132 recordings. The best-performing binary

classification model was a random forest model using the PLR parameters of latency, percent change, maximum diameter, minimum diameter, mean constriction velocity, and maximum constriction velocity as features. This model produced an overall accuracy of 93.5%, sensitivity of 96.2%, specificity of 90.9%, area under the curve of 0.936, and F_1-score of 93.7% for differentiating between pupillary changes in mTBI and healthy participants. The absolute values are unable to be provided for the performance percentages reported here due to the mechanism of 10-fold cross validation that was used to obtain them.

Conclusions: In this pilot study, quantitative smartphone pupillometry demonstrates the potential to be a useful tool in the future diagnosis of acute mTBI.

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KEYWORDS

smartphone pupillometry; pupillary light reflex; biomarkers; digital health; mild traumatic brain injury; concussion; machine learning; artificial intelligence; AI; pupillary; pilot study; brain; brain injury; injury; diagnostic; pupillometer; neuroimaging; diagnosis; artificial; mobile phone

Introduction

The pupillary light reflex (PLR) is a biomarker of neurological disease demonstrated by the reaction of the pupil to a light stimulus [1] that is commonly used in the management of moderate to severe traumatic brain injury (TBI) [2,3]. The pupil has both sympathetic and parasympathetic innervation that can be affected by mild TBI (mTBI). Traditional PLR assessment uses a manual penlight [4]; however, this method experiences poor interrater reliability, is highly subjective, and is of little use outside of moderate to severe TBI [4,5]. More recently, quantitative measurement of the PLR has been used as a biomarker for mTBI wherein the pupils are reactive but abnormal in a manner that is not easily detectable to the human eye [6]. Quantitative pupillometry is typically performed in the intensive care unit or in neuro–intensive care unit settings with United States Food and Drug Administration (FDA)–approved equipment (NeurOptics). There has been recent interest in the use of this same equipment for the diagnosis of concussion in military personnel after the blast injury [7], to document pupillary changes in those with chronic mTBI [8,9], and most recently interest in the diagnosis of sports-related concussions [10].

We developed a smartphone quantitative pupillometry app (PupilScreen) that measures the PLR with greater accuracy and higher interrater reliability than the manual penlight [11]. This study aims to investigate the ability of the smartphone pupillometry app to differentiate between participants with acute mTBI (<36 hours after injury) and healthy controls.

Methods

Recruitment

We used a previously developed binocular smartphone pupillometer (PupilScreen), which quantifies PLR curve morphological parameters (Textbox 1) to examine differences in pupillary reactivity between participants with acute mTBI and healthy participants. The smartphone pupillometry app requires a standard iPhone (Apple) camera without external hardware and is connected to a cloud-based neural network computer vision algorithm [11-15]. The app interface includes an augmented reality screen overlay with eye holes that helps to standardize the distance from the phone to the pupils for each measurement [13]. Using this technique in previous studies, the median error of pupil detection to the ground truth pupil diameter in millimeters was 0.23 and the mean absolute relative percent difference between sequential measurements was mean 5.8% (SD 3%) [12].

Patients with a clinical diagnosis of acute mTBI were enrolled prospectively through availability sampling (as this was an exploratory pilot study) in an emergency department after presenting with head trauma and known mechanism of injury less than 36 hours post injury from July 2022 to March 2023. mTBI was defined according to the American College of Rehabilitation Medicine (ACRM) criteria [16]. Participants were excluded if they had any intracranial abnormalities on neuroimaging. A separate cohort of healthy participants was enrolled from hospital staff using availability sampling over the same time period, which excluded those with self-reported known neurological disease or recent history of TBI.

Textbox 1. Definitions of pupillary light reflex parameters.

Latency (seconds [s]): time from onset of light stimulus to initial pupillary constriction
Percent change (%): percent change in pupillary diameter from maximum to minimum
Minimum pupillary diameter (pixels [px]): minimum diameter after light stimulus
Maximum pupillary diameter (px): average resting diameter before light stimulus
Mean constriction velocity (px/s): the average speed at which the pupil constricts after the light stimulus until the minimum diameter is reached
Maximum constriction velocity (px/s): the maximum speed at which the pupil constricts after the light stimulus until the minimum diameter is reached
Mean dilation velocity (px/s): the average speed at which the pupil dilates after removal of the light stimulus

Statistical Analysis

The PLR parameters were averaged for each subject between the left and right eyes before analysis. Differences in PLR parameters between cohorts were examined using a one-tailed *t* test for independent means. A *P* value of <.05 was considered statistically significant and a post hoc Bonferroni correction was implemented to control the probability of committing a type I error in the results. In addition, an analysis was performed to demonstrate the classification ability of the PLR parameters as feature inputs to machine learning models in the task of differentiating between the healthy and mTBI cohorts. Due to the significant class imbalance present, a synthetic minority oversampling technique (SMOTE) [17] was used to oversample the mTBI cohort PLR parameters to match the sample size of the healthy cohort. All PLR parameters were analyzed using 4 separate binary classification machine learning models: random forest, k-nearest neighbors, logistic regression, and support vector machine [18]. A 10-fold cross-validation stratified by cohort (which respects the independence of the training and testing sets) was used to produce the following model performance metrics, that are overall accuracy, sensitivity, specificity, area under the curve (AUC), and F_1-score, on the unseen test data sets. We report the best-performing feature combinations for each model type, based on AUC value, in differentiating PLR curves of patients with mTBI from healthy controls.

Ethical Considerations

This study was approved by the University of Washington institutional review board (#8009), and an informed consent process was followed for all participants as approved by the institutional review board.

Results

Cohort Characteristics

A total of 12 patients diagnosed with mTBI and 132 healthy participants were enrolled. Subject demographics are listed in Table 1 and characteristics of their injury are listed in Multimedia Appendix 1. Participants with acute mTBI were studied for an average of 6.8 (range 0.5-29) hours after injury. A total of 10 out of 12 in this sample had a loss of consciousness (<30 minutes) and 10 out of 12 had posttraumatic amnesia. Mechanisms of injury included motor vehicle collisions (n=2), motorcycle collisions (n=2), falls (n=6), and assaults (n=2).

Table 1. Demographic characteristics.

	Healthy (n=132)	mTBI[a] (n=12)
Age (years), mean (SD)	36 (10.2)	54.1 (22.3)
Sex, n (%)		
Female	88 (67)	4 (33)
Race or ethnicity, n (%)		
White	84 (64)	7 (58)
Asian	24 (18)	1 (8)
Black	12 (9)	2 (17)
Hispanic	8 (6)	2 (17)
Other	4 (3)	0 (0)
GCS[b], median	15	15[c]

[a]mTBI: mild traumatic brain injury.

[b]GCS: Glasgow Coma Scale.

[c]One subject had a GCS of 14.

Results of Statistical Analysis

Sample healthy and mTBI PLR curves produced by the smartphone app are shown in Multimedia Appendix 2. Significant differences were observed in PLR parameters of minimum diameter (*P*=.004), percent change, maximum diameter, and mean constriction velocity (*P*<.001; Table 2).

In the binary classification analysis, the SMOTE [17] produced a sample size of 132 mTBI PLR recordings and 132 healthy PLR recordings. The best-performing feature combinations based on AUC value across the 4 model types are listed in Table 3. The best-performing model overall was random forest, with the latency, percent change, minimum diameter, maximum diameter, mean constriction velocity, and maximum constriction velocity PLR parameters used as features. After stratified 10-fold cross-validation, this model produced an overall accuracy of 93.5%, sensitivity of 96.2%, specificity of 90.9%, AUC of 0.936, and F_1-score of 93.7% for differentiating between PLR curves of mTBI and healthy cohorts.

Table 2. Smartphone pupillometry PLR[a] parameters in healthy and participants with mTBI[b].

PLR parameters	Healthy, mean (SD)	Acute mTBI, mean (SD)	*P* value
Latency (s)	0.21 (0.075)	0.19 (0.12)	.17
Percent change (%)	34 (8.3)	26 (7.9)	<.001
Minimum pupillary diameter (pixels)	34.8 (6.1)	29.7 (6.1)	.004
Maximum pupillary diameter (pixels)	53.6 (12.4)	40.9 (11.9)	<.001
Mean constriction velocity (pixels/s)	11.5 (5.0)	6.8 (3.0)	<.001
Max constriction velocity (pixels/s)	48.9 (20.5)	38.7 (28.8)	.06
Mean dilation velocity (pixels/s)	5.4 (2.3)	3.9 (2.1)	.02

[a]PLR: pupillary light reflex.

[b]mTBI: mild traumatic brain injury.

Table 3. Best performing binary classification models[a].

Model	PLR[b] parameter combination	Accuracy, %	Sensitivity, %	Specificity, %	AUC[c]	F_1-score, %
RF[d]	Latency, percent change, maximum diameter, minimum diameter, mean constriction velocity, and maximum constriction velocity	93.5	96.2	90.9	0.936	93.7
KNN[e]	Percent change, maximum diameter, and minimum diameter	91.7	94.7	88.8	0.918	91.9
SVM[f]	Percent change, minimum diameter, mean constriction velocity, and mean dilation velocity	86	91	81	0.86	86.7
LR[g]	Maximum diameter, mean constriction velocity, and mean dilation velocity	86.3	95.5	77.4	0.864	87.7

[a]The absolute values are unable to be provided for the performance percentages reported here due to the mechanism of 10-fold cross-validation that was used to obtain them.

[b]PLR: pupillary light reflex.

[c]AUC: area under the curve.

[d]RF: random forest.

[e]KNN: k-nearest neighbors.

[f]SVM: support vector machine.

[g]LR: logistic regression.

Discussion

Principal Findings

We present data comparing PLR parameters (Textbox 1) in a cohort of patients with acute mTBI compared with healthy controls. Our results indicate that statistically significant differences can be detected between the mean PLR parameters of patients with acute mTBI and healthy controls using smartphone quantitative pupillometry. The percent change, minimum diameter, maximum diameter, and mean constriction velocity PLR parameters were significantly lower in the acute mTBI cohort (Table 2). This reflects the functional rather than structural abnormalities in neuronal homeostasis that are the basis of mTBI pathophysiology [19]. After using SMOTE [17] to resolve the class imbalance in our sample, we observed the performance of 4 binary classification models for differentiating between acute mTBI and healthy controls (Table 3), the best of which produced accuracy, sensitivity, specificity, AUC, and F_1-score all above 90%, suggesting useful diagnostic discrimination.

Comparison With Previous Work

There has been increased interest in PLR as a physiologic biomarker of mTBI and in automated pupillometry. One study of the NPi-200 commercial pupillometry device in patients with blast-induced mTBI 15-45 days post injury found that mean constriction velocity, latency, and mean dilation velocity were slower than controls [7]. A follow-up study of 100 soldiers with a concussion compared with 100 controls without a concussion <72 hours post injury had similar findings [20]. Pupillary changes have also been demonstrated in those with chronic mTBI compared with controls >45 days and >1 year post injury using automated quantitative pupillometry [8,9]. Most recently, changes in pupillary reactivity were demonstrated in 98 youths with a concussion compared with 134 controls at a median of 12 days post injury [10]. Smartphone apps have also been studied previously in the diagnosis and management of concussion and mTBI based on subjective clinical findings

[21-23], although before this study, only 1 used pupillometry [24].

Detailed Discussion of This Work

The smartphone pupillometer used in this study (PupilScreen) has several advantages over more traditional devices. It is more affordable and would be more accessible and practical in clinical care settings outside of the hospital. It also has demonstrated improved performance when compared with a proprietary pupillary reactivity index [25] in the setting of severe TBI [14], without effects from opioid medication use [15]. The smartphone pupillometer in this study has also shown potential use in the diagnosis of other neurological conditions such as in the detection of acute preintervention ischemic stroke while a proprietary pupil index [25] remained within the normal and reactive range for all participants who had stroke [13]. Other quantitative pupillometry technologies have been studied with varying hardware and software features and requirements [25-29], yet these technologies have not been studied as extensively, do not support simultaneous binocular recording of the PLR for dynamic assessment, and do not incorporate machine learning to uncover nuanced relationships between PLR parameters that may not be easily summarized in a proprietary reactivity index [25].

In this study, we observed alterations of the autonomic nervous system in mTBI compared with healthy controls (reduction in maximum and minimum pupil diameters) and direct effects of mTBI functional pathophysiology on cranial nerve III or its postganglionic short ciliary nerve derivatives [1] (difference in percent change and mean constriction velocity parameters). These results correlate with previous studies in acute mTBI [20] on the importance of the mean constriction velocity but not on that of the mean dilation velocity, which may be due to mechanical differences in the method of capture between other quantitative pupillometers and the smartphone quantitative pupillometer used in this study. A report of patients with chronic mTBI demonstrated findings similar to our study (despite evaluating chronic, rather than acute mTBI), finding significant differences seen in the maximum resting pupillary diameter, mean constriction velocity, maximum constriction velocity, mean dilation velocity, and percent change PLR parameters [8]. Our study is unique in that it includes only participants within 36 hours after injury, unlike others for which recruitment occurred up to several weeks after mTBI [7-10], and in that it uses smartphone pupillometry as an accessible and practical alternative to traditional quantitative pupillometry.

Using Multimedia Appendix 2 as an example, PLR curves between a healthy control and a patient with acute mTBI look subjectively similar to the naked eye. Despite this, a statistically significant difference was found in the structural curve morphology parameters listed above, indicating that using these quantitative PLR parameters in combination (rather than each one alone) may be necessary to detect subtle changes that may be present in acute mTBI. The results of our binary classification models support this, as when the PLR parameters are used in combination with one another as features in a machine learning binary classification model, we see a reasonable capability of the model to differentiate between healthy and participants with acute mTBI with more than 90% on all model performance metrics. In addition, the important PLR parameters mirror those from the literature and our individual parameter comparison results. While preliminary, our results show promise in the usage of a mobile smartphone pupillometer with advanced PLR analysis to detect mTBI, which could have major implications in fields such as athletics, prehospital care, the military, and digital health in general. Although we did not evaluate the diagnostic spectrum of mild, moderate, and severe TBI in this pilot study, such work is ongoing using the smartphone pupillometer studied here. In addition, we believe that there is value in studying an objective tool for acute mTBI differentiation from healthy controls as it has been demonstrated in the literature that cases of acute mTBI are missed in the acute care setting (such as the emergency department setting where this study was conducted) [30,31].

Limitations

This study is limited by multiple factors, the first of which is the small sample size of 12 patients with acute mTBI. We have addressed this limitation through our use of SMOTE [17] to equalize the sample size of both cohorts to 132 recordings for binary classification machine learning analysis, nonetheless, larger studies are required for external validation and there is a risk of overfitting in the machine learning models when using this approach. Another limitation of this approach is the possibility that the sample of patients with acute mTBI is not representative of the broader acute mTBI population. Using the case descriptions in Multimedia Appendix 1, a heterogeneous distribution of case types is seen with a wide range in time after injury, a variety of mechanisms (falls, assaults, and motor vehicle collisions), and findings on examination that are qualifying for the ACRM definition of acute mTBI. Thus, we believe that despite the small sample size, we have captured a somewhat representative group of the broader emergency department population with acute mTBI using availability sampling. Another limitation is the mechanism of injury, which was entirely mechanically induced, which may limit the application of our findings to participants with blast-induced injury in military settings [7]. Finally, our healthy cohort was younger than the acute mTBI cohort, and thus known changes in the PLR along the spectrum of aging [32] may have affected our results.

Conclusions

In this pilot study, mobile pupillometry using a smartphone app detected significant differences in PLR parameters and performed with greater than 90% accuracy, sensitivity, specificity, AUC, and F_1-score on binary classification between acute mTBI and healthy cohort. The technology studied in this pilot study may have potential future use in hospital or nonhospital settings to detect acute mTBI and concussion after future validation to test the generalizability and stability of its predictions on prospectively collected external testing data sets.

Conflicts of Interest

MRL is a consultant for Apertur, Medtronic, Aeaean Advisers, Metis Innovative, Stereotaxis; has equity interest in Apertur, Proprio, Stroke Diagnostics, Synchron, Hyperion Surgical, Fluid Biomed; and is on the Editorial board of Journal of NeuroInterventional Surgery. AJM has equity interest in Apertur. LBM is the cofounder with an equity interest in Apertur.

Multimedia Appendix 1
Table – Injury Characteristics.
[DOCX File , 15 KB - neuro_v3i1e58398_app1.docx]

Multimedia Appendix 2
Acute mTBI (A) and healthy subject (B) pupillary light reflex (PLR) curves. Top panel: PLR curve of right (red) and left (blue) eyes. Bottom panel: Brightness of the recording as detected by the smartphone camera. Although some motion artifact is present in both curves, the mTBI and healthy subject curves appear qualitatively similar with pupillary constriction during increased brightness (due to the light stimulus from the smartphone camera flash) and pupillary re-dilation towards baseline diameter after cessation of light stimulus. Brightness is a unitless measurement of the ambient brightness detected by the built-in iPhone camera during the entire recording of the PLR. It is reported in APEX (Additive System of Photographic Exposure) which is an iPhone-specific measurement; more details can be found in iPhone software documentation.
[PNG File , 401 KB - neuro_v3i1e58398_app2.png]

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Abbreviations

ACRM: American College of Rehabilitation Medicine
AUC: area under the curve
FDA: United States Food and Drug Administration
mTBI: mild traumatic brain injury
PLR: pupillary light reflex
SMOTE: synthetic minority oversampling technique
TBI: traumatic brain injury

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Original Paper

Validity of a Smartphone App to Objectively Monitor Performance Outcomes in Degenerative Cervical Myelopathy: Preliminary Findings From a Longitudinal Observational Study

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Abstract

Background: Developing new clinical measures for degenerative cervical myelopathy (DCM) is an AO Spine RECODE-DCM research priority. Difficulties detecting DCM, and changes in DCM, cause diagnostic and treatment delays in clinical settings and heightened costs in clinical trials due to elevated recruitment targets. Digital outcome measures can tackle these challenges due to their ability to measure disease remotely, repeatedly, and more economically.

Objective: The study aims to assess the validity of MoveMed, a battery of performance outcome measures performed using a smartphone app, in the measurement of DCM.

Methods: A prospective observational study in decentralized secondary care was performed in England, United Kingdom. Validity and risk of bias were assessed using criteria from the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) manual. Each MoveMed outcome was compared with 2 patient-reported comparators, with a priori hypotheses of convergence or divergence tested against consensus thresholds. The primary outcome was the correlation coefficient between the MoveMed outcome and the patient-reported comparators. The secondary outcome was the percentage of correlations that aligned with the a priori hypotheses. The comparators used were the patient-derived modified Japanese Orthopaedic Association score and the World Health Organization Quality of Life Brief Version questionnaire. Thresholds for convergence or divergence were set at ≥0.3 for convergence, <0.3 for divergence, and >0/<0 for directionality.

Results: A total of 27 adults aged 60 (SD 11) years who live with DCM and possess an approved smartphone were included in a preliminary analysis. As expected, MoveMed tests of neuromuscular function correlated most with questionnaires of neuromuscular function (≥0.3) and least with questionnaires of quality of life (<0.3). Furthermore, directly related constructs correlated positively to each other (>0), while inversely related constructs correlated negatively (<0). Overall, 74% (67/90) and 47% (8/17) of correlations (unidimensional and multidimensional, respectively) were in accordance with hypotheses. No risk-of-bias factors from the COSMIN Risk of Bias checklist were recorded. Overall, this was equivalent to "very good" quality evidence of sufficient construct validity in DCM.

Conclusions: MoveMed outcomes and patient-reported questionnaires converge and diverge in accordance with expectations. These findings support the validity of the MoveMed tests in an adult population living with DCM. Criteria from COSMIN provide "very good" quality evidence to support this.

(JMIR Neurotech 2024;3:e52832) doi:10.2196/52832

KEYWORDS

validation study; patient outcome assessment; smartphone; neurology; psychometrics; validity; validation; outcomes; degenerative; myelopathy; neuroscience; spine; monitor; monitoring; neuromuscular; muscular; mHealth; apps; measure; measures; measurements

Introduction

Abnormal limb movement is a key phenotype of disease affecting the nervous and musculoskeletal systems. Loss of dexterity, for example, is a notable manifestation of conditions such as Parkinson disease, degenerative cervical myelopathy (DCM), peripheral neuropathy, and osteoarthritis [1,2]. The significance of this phenotype can be seen in the physician's approach to examining the neuromuscular systems, the features used to distinguish or measure its disease, or the information sought to define its care and research. Collectively, diseases affecting the nervous and musculoskeletal systems are estimated to account for 1.1 to 4.9 million deaths and 165 to 357 million disability-adjusted life year (DALYs) worldwide and are the leading causes of global disability, reflecting their often chronic nature [3-5].

While abnormal movement is a key component of diagnosis, it is also a key component of longitudinal monitoring, as these diseases typically lack responsive serological or imaging biomarkers [6]. Such monitoring is key to adjusting or reviewing treatment strategies over time and defining the success or failure of research trials [7]. Today, monitoring relies on qualitative outcome measures: classifications based on a hierarchy of exemplar functions, such as questionnaires or item selection. While qualitative tools can be robust, valid, and even performed by the patient remotely, their limited granularity and intrinsic subjectivity mean they lack accurate and responsive discrimination of small but significant changes, particularly for fluctuating diseases [8]. For clinical care, this means clinically important change is seen late, often at the cost of increased disability [9]. For clinical research, the low statistical power of qualitative tools means far higher sample sizes are needed for trials to mitigate type 2 errors.

This is exemplified within DCM, a slow-motion spinal cord injury estimated to affect 1 in 50 adults [10-13]. Here, dexterity, gait, and balance are key measurement constructs [14]. Currently, the gold-standard outcome measure is the modified Japanese Orthopaedic Association (mJOA) score, but it is poorly responsive [6]. Further, score variation, driven partly by the disease and partly by reliability, is more than twice the minimal clinically important difference. In practice, this demands sample sizes greater than 300 patients for 1:1 comparison with at least 80% power [15,16]. Developing new approaches to functional measurement is a recognized research priority [14].

Advances in our ability to assess limb performance can thus greatly improve our understanding of the patient's clinical picture, lead to better decision-making and outcomes, as well as accelerate knowledge discovery [17,18]. The sensors contained within smartphones offer the potential to achieve this. Smartphones are increasingly carried by all patient groups, with far greater penetrance and priority than other wearable devices such as smartwatches [19]. Current focus in portable technology with respect to health has largely been on "background monitoring," but shortcomings remain, including accurate and responsive insights at the individual patient level, as well as between-device variation [20].

This study evaluates MoveMed, a smartphone app originally developed by researchers from the University of Cambridge to assess hand, arm, and leg function in real-time, in the user's natural environment, and under standardized conditions. This approach is, therefore, different from background monitoring: it harnesses the accuracy of mobile sensors to measure movement but does so during prescribed activities or tasks, designed by health care professionals and patients to target critical markers of disease. It can therefore be considered a patient-performed, performance-based outcome (PerfO) or performance-based outcome measure (PerfOM). Since MoveMed is being developed in accordance with ISO 13485 (Software as a Medical Device), testing of measurement properties was timely given recent laboratory experience of technological readiness (TRL4). In terms of V3 stages for biometric monitoring technologies [21], the testing in this paper corresponds to clinical validation.

MoveMed was originally developed for DCM. Therefore, the focus of this report is on the validity of the MoveMed battery of PerfOMs in DCM. However, recognizing that the measurement constructs in this disease are shared across other neuromuscular diseases, its validity is currently being explored in other conditions. Formal methods and criteria from the US Food and Drug Administration and COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments)

guidelines were used to design a prospective and decentralized observational study. Validity and risk of bias were principally assessed via hypothesis testing of construct validity. Content validity will be formally evaluated separately but is briefly described in this work. This paper is the first of a series of clinimetric studies about the measurement properties of MoveMed battery of PerfOMs.

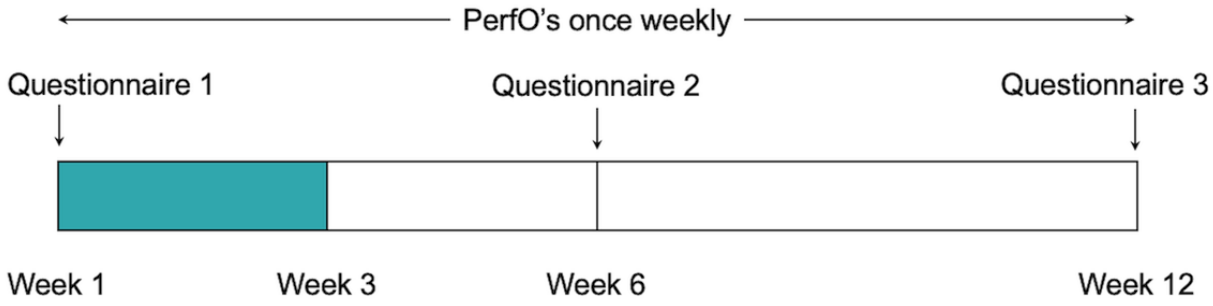
Methods

Participants

Between September 2022 and April 2023, a total of 27 people with DCM were enrolled in the prospective and decentralized EMPOWER study [22]. Prospective participants were recruited via a web-based campaign and asked to complete consent and registration forms (Figure 1) [23,24]. These were used to screen participants for eligibility. Participants were deemed eligible if they had a self-reported diagnosis of DCM, owned a smartphone, and were able to stand and walk without the assistance of another person. Eligible participants were invited to download the MoveMed app to their smartphones and complete an electronic, baseline questionnaire on neuromuscular function, hand dominance, and quality of life. This included questions from the patient-derived mJOA (P-mJOA) and the World Health Organization Quality of Life Brief Version (WHOQOL-Bref).

All enrolled participants were asked to perform each task in the MoveMed app once per week for a period of 12 weeks. Task adherence was remotely monitored once a week using a bespoke web-based dashboard. Participants were offered reminders and help via email once a week if 14 days passed since the completion of the latest task. These were offered a total of 2 consecutive times per participant, after which the participant was considered lost to follow-up. At weeks 6 and 12, participants were asked to complete the same electronic questionnaire from week 1.

Figure 1. Study timeline. Data from the first 3 weeks of the study were included in this analysis due to the ongoing status of the trial. PerfO: performance-based outcome.



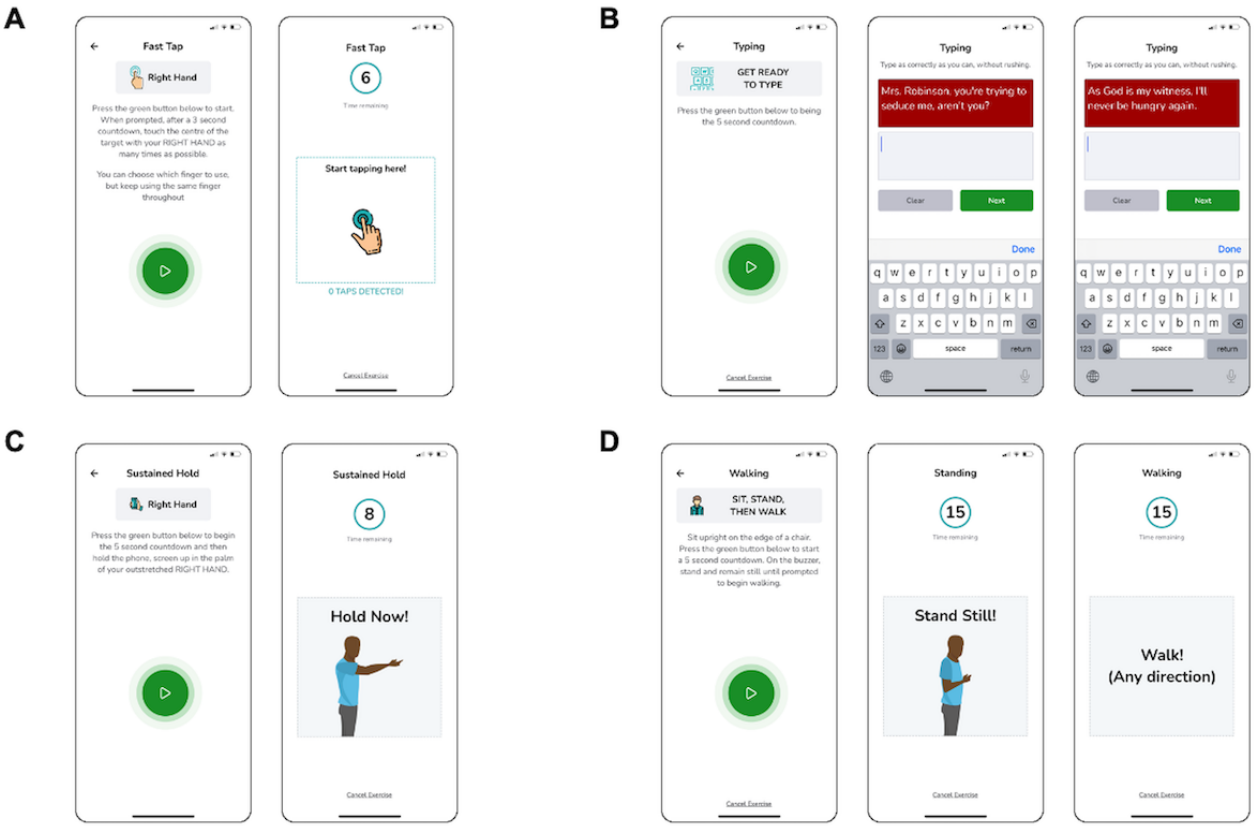
MoveMed and Tasks

MoveMed is a smartphone app designed by academic neurosurgeons and computer scientists from the University of Cambridge to administer PerfOMs (Figure 2). These may be administered by clinicians during in-person visits or self-performed by individuals in the community. Version 1.0.0 of the app originally offered 3 performance tasks: a fast tap test, a hold test, and a stand and walk test. Version 1.2.2 incorporated an additional offering—a typing test—while making no changes to the 3 original tasks. Versions 1.0.0 and 1.2.2 were available in the Android Google Play Store and iOS App Store, respectively, at the time of writing and were used in this study by enrolled participants.

The fast tap test is a unidimensional PerfO task that assesses finger dexterity through a 6-second smartphone touch-based task. Users are shown a demonstrative cartoon (Figure 2A) and instructed to "touch the center of the target with [each] hand as many times as possible." In-app video demonstration is also available. The construct (finger dexterity) is assessed by measuring the speed, accuracy, and efficiency of finger tapping as continuous variables and analyzing them as a panel of unidimensional measures. Content validity was assessed by AYT, MRNK, and BMD through literature review and clinical and patient input and deemed relevant, comprehensive, and comprehensible at the time of development [25-27]. In this study, tap latency was used as a reflective measure of finger dexterity.

The typing test is another unidimensional PerfO task that assesses finger dexterity through a 2-stage smartphone touch-based task. Users are shown a demonstrative cartoon (Figure 2B) and instructed to "type as correctly as they can, without rushing." In-app video demonstration is also available. The construct (finger dexterity) is assessed by measuring the speed, accuracy, and efficiency of typing as continuous variables and analyzing them as a panel of unidimensional measures. Content validity was assessed by AYT, MRNK, and BMD through literature review and clinical and patient input and deemed relevant, comprehensive, and comprehensible at the time of development [25-27]. In this study, typing speed was used as a reflective measure of finger dexterity.

Figure 2. Schematic illustrations of the MoveMed battery of performance outcome measures. (A) The 6-second fast tap test; (B) the 2-stage typing test; (C) the 8-second hold test; and (D) the 15-second stand and walk test.



The hold test is a unidimensional PerfO task that assesses upper limb stability through an 8-second in-hand smartphone task. Users are shown a demonstrative cartoon (Figure 2C) and instructed to "hold the phone, screen up in the palm of [their] outstretched hand." In-app video demonstration is also available. The construct (upper limb stability) is assessed by measuring the involuntariness, rhythmicity, and oscillation of the upper limbs as continuous variables and analyzing them as a multidimensional Stability Score. Content validity was assessed by AYT, MRNK, and BMD through literature review and clinical and patient input and deemed relevant, comprehensive, and comprehensible at the time of development [25-27]. In this study, the Stability Score was used as a reflective measure of upper limb stability.

The stand and walk test is a multidimensional PerfO task that assesses gait through a 2-stage in-hand smartphone task. During the first stage, users are instructed to "sit upright on the edge of a chair [and to] press the green button [when they are ready to] stand and remain still." During the second stage, users are instructed to "walk [in] any direction." In-app cartoons and video demonstrations are also available (Figure 2D). The construct (gait) may then be assessed by measuring standing or walking as continuous variables and analyzing them as multidimensional measures. Content validity was assessed by AYT, MRNK, and BMD through literature review and clinical and patient input and deemed relevant, comprehensive, and comprehensible at the time of development [25-27]. In this study, cadence was used as a reflective measure of gait.

Patient-Reported Comparators

The 2 patient-reported outcomes (PROs) or PRO measures (PROMs) were used as comparators for DCM: the P-mJOA and the WHOQOL-Bref.

The P-mJOA score is a multidimensional, patient-reported questionnaire that assesses neuromuscular function in DCM across 4 items: motor dysfunction of the upper extremities (MDUE), motor dysfunction of the lower extremities (MDLE), sensory function of the upper extremities, and sphincter dysfunction [28]. Responses are scored on an ordinal scale per item and presented as both a panel of unidimensional scores and an unweighted sum-total, multidimensional score. The P-mJOA score was selected due to the existence of a systematic assessment of construct validity (r>0.5) and feasibility in DCM [6] and due to the use of its clinically reported analog (the mJOA) as the current gold standard. The P-mJOA score was favored over the mJOA score since it is intended to be a truly patient-reported equivalent of the mJOA score, which can be understood by individuals with no medical knowledge or training [29].

The WHOQOL-Bref is a multidimensional, patient-reported questionnaire that assesses quality of life across 26 items grouped into 4 domains: physical health, psychological health, social relationships, and environmental health [30]. Responses are scored on a 5-point ordinal scale per item and presented as a panel of sum-total, multidimensional scores. Responses to 2 items may, furthermore, be presented individually to give insight into the respondent's global perception of their quality of life and their quality of health. These were presented in writing to

describe the population's characteristics but were not considered robust enough to warrant correlation analysis. The WHOQOL-Bref was selected due to the existence of systematic assessments of validity, reliability, and responsiveness in traumatic brain injury [31], Parkinson disease [32], and DCM [6]. It was also favored over the 36-Item Short Form Health Survey due to its relative brevity and over the EuroQOL Five Dimensions Questionnaire due to licensing restrictions.

Statistical Analysis

The COSMIN manual defines validity as "the degree to which [an instrument] measures the construct it purports to measure" [33]. In the absence of a gold standard, validity may be assessed formally through hypotheses testing of correlations to known standards. These may then be judged both as a panel of stand-alone ratings [34].

In this study, we assessed validity by correlating the MoveMed PerfOs to their corresponding patient-reported comparators. This was achieved by comparing it to the P-mJOA and WHOQOL-Bref PROMs. Due to the ongoing status of the trial, data from the first 3 weeks of the study were included (Figure 1). All available tests within this period were included. Longitudinal replicates of MoveMed tasks were averaged before comparing their mean scores to the mean scores of the PROMs. Responses from the baseline questionnaire were used and results were subgrouped by diagnosis. Missing data were not imputed, and all analyses were done using Python (version 3.10.12; Python Software Foundation).

The goal of the analysis was to determine "whether the direction and magnitude of a correlation is similar to what could be expected based on the constructs that are being measured" [33,35]. Spearman rank correlation coefficients (ρ) were thus computed due to their suitability for ordinal scales. In accordance with COSMIN, *P* values were not used "because it is not relevant to examine whether correlations statistically differ from zero" [33,35]. Hypotheses about the direction and magnitude of correlations were instead drawn and adapted from COSMIN [33] and de Vet et al [36]. We hypothesized that the magnitude of correlations between outcomes measuring similar constructs should be ≥0.5; the magnitude of correlations between outcomes measuring related, but dissimilar, constructs should be ≥0.3, and ideally <0.5; the magnitude of correlations between outcomes measuring unrelated constructs should be <0.3; and the direction of correlations between outcomes measuring directly related constructs should be positive (>0) and negative (<0) between outcomes measuring inversely related constructs.

As reported in Yanez Touzet et al [6], constructs were defined as "similar" if they both measured the same domain with a unidimensional instrument. If they measured the same domain, but at least 1 of the instruments was multidimensional, the constructs were defined as "related but dissimilar." Constructs measuring different domains were otherwise defined as "unrelated."

Risk-of-Bias Assessment

The COSMIN Risk of Bias checklist 9a [33] was used to assess the methodological quality of hypotheses testing.

Overall Assessment

Overall assessments of construct validity were made using a panel of ratings and prior knowledge of content validity. These were appraised qualitatively and presented in writing due to the relatively higher importance of some comparators over others. As in COSMIN [33], correlations were converted into ratings by comparing results to hypotheses. Correlations in accordance with hypotheses were rated "sufficient." Correlations in opposition were rated "insufficient." Correlations in between boundaries (eg, ρ=0) and statistical artifacts (eg, nonmonotonic data) were rated "indeterminate."

Ethical Considerations

This study was independently assessed and approved by the University of Cambridge (HBREC.2022.13). All study participants provided informed consent before enrolling in the study and were able to opt out at any point. Study data were anonymized. None of the participants received any form of compensation for enrolling in or completing the trial.

Results

Participants

A total of 27 participants with DCM enrolled in the prospective and decentralized EMPOWER study (Figure 3), principally via advertisement through Myelopathy.org, a DCM charity [23,24]. On average, participants were aged 60 (SD 11) years (Table 1). DCM severity ranged from mild to severe (P-mJOA total score range 8-18). The impact on upper limb motor function ranged from none to "unable to eat with spoon but able to move hands" (P-mJOA MDUE subscore range 2-5) and the impact on lower limb motor function ranged from none to "able to move legs but unable to walk" (P-mJOA MDLE subscore range 2-7). Overall health perception ranged from "satisfied" to "very dissatisfied" (WHOQOL overall health range 1-4), and overall quality of life perception ranged from "very good" to "very poor" (WHOQOL overall quality of life range 1-5). In terms of the MoveMed PerfOs, participants paused for 80-2600 ms in between taps and typed approximately 0.6-2.5 keys per second. Arm stability ranged from 39% to 100% and cadence ranged from 14 to 112 steps per minute.

Differential app use was noted throughout the studied period (Table 2). More participants used the stand and walk and typing tests (n≥20) than the fast tap and hold tests (n≥12). However, mean adherence was higher with the fast tap and hold tests (100% and 90%, respectively) than with the stand and walk and typing tests (77% and 72%, respectively). Crucially, median adherence was satisfactory: 100% for the fast tap, hold, and stand and walk tests, and 80% for the typing test. Differential use was thus attributed to individual test preferences.

Figure 3. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram. DCM: degenerative cervical myelopathy.

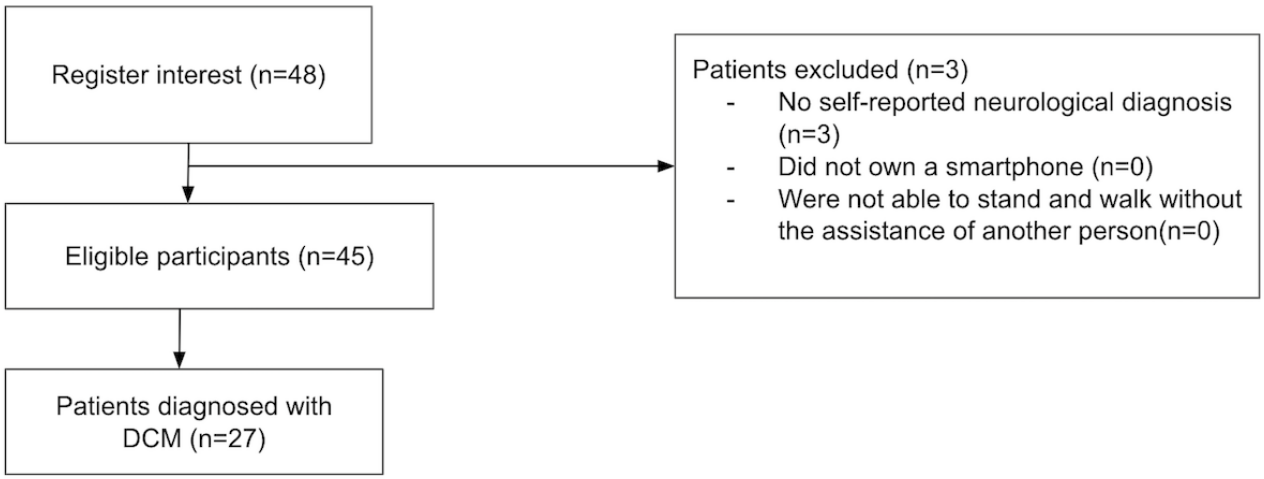


Table 1. Characteristics of study participants (N=27).

Feature	Value
Participants, n (%)	27 (100)
Age (years), mean (SD)	60.7 (10.8)
P-mJOA[a] score (reference range 0-18), mean (SD)	11.4 (2.9)
MDUE[b] (reference range 0-5)	3.4 (1.1)
MDLE[c] (reference range 0-7)	4.1 (1.3)
SDUE[d] (reference range 0-3)	1.6 (0.8)
SD[e] (reference range 0-3)	2.3 (0.7)
WHOQOL-Bref[f] score, mean (SD)	
Overall QOL[g] (reference range 1-5)	2.9 (1.1)
Overall health (reference range 1-5)	2.6 (0.8)
EH[h] (reference range 8-40)	25.5 (5.5)
PH[i] (reference range 7-35)	18.6 (5.6)
PS[j] (reference range 6-30)	18.6 (4.1)
SR[k] (reference range 3-15)	9.2 (2.1)
MoveMed fast tap test intertap duration[l] (s), mean (SD)	0.24 (0.13), 0.36 (0.52)
MoveMed hold test Stability Score[l] (%), mean (SD)	78.6 (16.0), 75.8 (15.1)
MoveMed typing test speed (keys per second), mean (SD)	1.39 (0.42)
MoveMed stand and walk test cadence (steps per minute), mean (SD)	58.8 (26.9)

[a]P-mJOA: patient-derived modified Japanese Orthopaedic Association.
[b]MDUE: motor dysfunction of the upper extremity.
[c]MDLE: motor dysfunction of the lower extremity.
[d]SDUE: sensory dysfunction of the upper extremity.
[e]SD: sphincter dysfunction.
[f]WHOQOL-Bref: World Health Organization Quality of Life Brief Version
[g]QOL: quality of life.
[h]EH: environmental health,
[i]PH: physical health.
[j]PS: psychological health.
[k]SR: Social relationships.
[l]Data reported as “dominant hand, nondominant hand” mean (SD) pairs. Ranges are reported elsewhere in the paper.

Table 2. Correlations, ratings, and hypotheses for construct validity testing.

MoveMed outcome measure and comparator	Hypotheses		Result[a]	Total	Rating[b]		ROB[c]
	Direction	Magnitude			Direction	Magnitude	
MoveMed fast tap test (rating proportion in correspondence: Direction 9/9, 8/9; Magnitude 4/9, 4/9)							
P-mJOA[d] total score	$r < 0$	$0.3 \leq \lvert r \rvert (< 0.5)$	–0.47, –0.42	12	+, +	+, +	No
P-mJOA MDUE[e] subscore	$r < 0$	$\lvert r \rvert \geq 0.5$	–0.28, –0.40	12	+, +	–, –	No
P-mJOA MDLE[f] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.42, –0.18	12	+, +	–, +	No
P-mJOA SDUE[g] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.28, –0.36	12	+, +	+, –	No
P-mJOA SD[h] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.54, –0.44	12	+, +	–, –	No
WHOQOL[i]-Bref EH[j] subscore	$r < 0$	$\lvert r \rvert < 0.3$	+0.21, –0.05	12	+, –	+, +	No
WHOQOL-Bref PH[k] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.39, –0.38	12	+, +	–, –	No
WHOQOL-Bref PS[l] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.64, –0.43	12	+, +	–, –	No
WHOQOL-Bref SR[m] subscore	$r < 0$	$\lvert r \rvert < 0.3$	–0.15, –0.20	12	+, +	+, +	No
MoveMed hold test (rating proportion in correspondence: Direction 8/9, 9/9; Magnitude 5/9, 4/9)							
P-mJOA total score	$r > 0$	$0.3 \leq \lvert r \rvert (< 0.5)$	+0.02, +0.55	13	+, +	–, +	No
P-mJOA MDUE subscore	$r > 0$	$\lvert r \rvert \geq 0.5$	+0.14, +0.64	13	+, +	–, +	No
P-mJOA MDLE subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.13, +0.36	13	+, +	+, –	No
P-mJOA SDUE subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.21, +0.47	13	+, +	+, –	No
P-mJOA SD subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.45, +0.14	13	+, +	–, +	No
WHOQOL-Bref EH subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.14, +0.31	21	+, +	+, –	No
WHOQOL-Bref PH subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.16, +0.43	21	+, +	+, –	No
WHOQOL-Bref PS subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.18, +0.02	21	–, +	+, +	No
WHOQOL-Bref SR subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.31, +0.47	21	+, +	–, –	No
MoveMed typing test (rating proportion in correspondence: Direction 9/9; Magnitude 7/9)							
P-mJOA total score	$r > 0$	$0.3 \leq \lvert r \rvert (< 0.5)$	+0.38	20	+	+	No
P-mJOA MDUE subscore	$r > 0$	$\lvert r \rvert \geq 0.5$	+0.37	20	+	–	No
P-mJOA MDLE subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.21	20	+	+	No
P-mJOA SDUE subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.32	20	+	–	No
P-mJOA SD subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.07	20	+	+	No
WHOQOL-Bref EH subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.08	20	+	+	No
WHOQOL-Bref PH subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.17	20	+	+	No
WHOQOL-Bref PS subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.15	20	+	+	No
WHOQOL-Bref SR subscore	$r > 0$	$\lvert r \rvert < 0.3$	+0.10	20	+	+	No
MoveMed stand and walk test (rating proportion in correspondence: Direction 1/9; Magnitude 7/9)							
P-mJOA total score	$r > 0$	$0.3 \leq \lvert r \rvert (< 0.5)$	–0.04	21	–	–	No
P-mJOA MDUE subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.17	21	–	+	No
P-mJOA MDLE subscore	$r > 0$	$0.3 \leq r (< 0.5)$	+0.35	22	+	+	No
P-mJOA SDUE subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.18	21	–	+	No
P-mJOA SD subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.14	21	–	+	No
WHOQOL-Bref EH subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.28	21	–	+	No
WHOQOL-Bref PH subscore	$r > 0$	$\lvert r \rvert < 0.3$	–0.12	21	–	+	No

MoveMed outcome measure and comparator	Hypotheses		Result[a]	Total	Rating[b]		ROB[c]
	Direction	Magnitude			Direction	Magnitude	
WHOQOL-Bref PS subscore	$r > 0$	$\|r\| < 0.3$	0.00	21	?	+	No
WHOQOL-Bref SR subscore	$r > 0$	$\|r\| < 0.3$	–0.31	21	–	–	No

[a]Data reported as single "ρ" values or "dominant hand, nondominant hand" ρ pairs.

[b]"+"=Sufficient; "?"=Indeterminate. Data reported as single ratings or "dominant hand, nondominant hand" rating pairs; "–"=Insufficient.

[c]ROB: risk of bias.

[d]P-mJOA: patient-derived modified Japanese Orthopaedic Association.

[e]MDUE: motor dysfunction of the upper extremity.

[f]MDLE: motor dysfunction of the lower extremity.

[g]SDUE: sensory dysfunction of the upper extremity.

[h]SD: sphincter dysfunction.

[i]WHOQOL-Bref: World Health Organization Quality of Life Brief Version

[j]EH: environmental health.

[k]PH: physical health.

[l]PS: psychological health.

[m]SR: social relationships.

Patient-Reported Comparators

Spearman rank correlation coefficients are reported in Table 2. As expected, correlations were positive between PerfOs and PROs measuring directly related constructs (eg, hold and typing tests vs P-mJOA and WHOQOL-Bref) and negative between PerfOs and PROs measuring inversely related constructs (eg, fast tap test vs P-mJOA and WHOQOL-Bref). This was most pronounced in the fast tap, hold, and typing tests.

Correlation magnitudes were, furthermore, highest between PerfOMs and PROMs of neuromuscular function (eg, fast tap test vs P-mJOA≥0.3) and lowest between PerfOMs and PROMs of quality of life (eg, fast tap test vs WHOQOL-Bref<0.3).

This was also in accordance with expectation and was most pronounced in the fast tap, hold, and typing tests.

Correlation magnitudes were notably low (<0.3) in the stand and walk test. This could be due to it being the only multidimensional PerfOM in the battery. Importantly, correlation with the lower limb comparator domain (ie, the P-mJOA MDLE subscore) was the highest, in accordance with expectation.

Risk-of-Bias Assessment

No risk of bias factors from the COSMIN Risk of Bias checklist were recorded (Multimedia Appendix 1). This was equivalent to a "very good" rating for methodological quality [33].

Overall Assessment

Hypotheses and result ratings are also reported in Table 2. These are appraised in writing due to the relatively higher weight of some comparators over others.

Overall, 74% (67/90) of correlations for the fast tap, hold, and typing tests were in correspondence with hypotheses (Table 2). This provides robust evidence for the validity of these PerfOMs in the assessment of DCM: particularly due to the relatively higher importance of the correlations to the upper limb comparator (ie, the P-mJOA MDUE subscore), which were concordant. For the stand and walk test, 47% (8/17) of the correlations were in correspondence with the hypotheses. This also provides preliminary evidence for the validity of this PerfOM in the assessment of DCM: particularly due to the relatively higher importance of the correlation to the lower limb comparator (ie, the P-mJOA MDLE subscore), which was concordant. Taken together, these data provide "very good" quality evidence for the overall validity of the PerfOMs in the assessment of DCM.

Discussion

Principal Findings

Smartphone apps are increasingly being used to administer clinical outcome measures in medicine. This study used consensus-based standards to assess the validity of an app designed by neurosurgeons and computer scientists from the University of Cambridge. A total of 2 lines of evidence were produced: first, a panel of correlations between the app's tasks and established clinical comparators, and second, a panel of ratings made in accordance with prespecified hypotheses. The former produced modular evidence of construct validity and the latter a means for its overall appraisal. This type of evidence corresponds to clinical validation under the V3 framework for biometric monitoring technologies and succeeds in laboratory-based verification and analytical validation [21].

Construct validity uses comparison to other measures to assess validity. Where comparators take different approaches or contain their own limitations, validity should not be defined by traditional correlation thresholds [37]. This is applicable to DCM, where we are trying to improve disease measurement. For example, we recognize the mJOA score as a gold standard measure of disease severity, but it measures multiple constructs with limited discrimination, particularly of milder diseases. If a new measure has a correlation of 1.0 with an existing measure, it indicates that the 2 instruments are equivalent, which suggests it is unlikely to offer any improvement. For assessing construct

validity, it is therefore preferable to explore expected relationships through hypothesis testing. As expected, the direction and magnitude of MoveMed correlations were most convergent between tasks and questionnaires measuring similar constructs than tasks and questionnaires measuring dissimilar constructs (eg, fast tap test vs P-mJOA > fast tap test vs WHOQOL-Bref). This is because neuromuscular tasks should correlate more with neuromuscular constructs than with non-neuromuscular ones (eg, finger dexterity vs upper extremity neuromuscular function > finger dexterity vs quality of life) and because unidimensional tasks should correlate more with other unidimensional measures than with multidimensional ones (eg, unidimensional vs unidimensional>unidimensional vs multidimensional).

To enable performance across correlations to be judged, a proportion of overall hypothesis agreement may be used [34]. After rating, 74% (67/90) and 47% (8/17) of unidimensional and multidimensional results, respectively, were deemed sufficient for construct validity in the DCM subgroup. In the absence of risk of bias factors, these data provide “very good” quality evidence for the validity of MoveMed tasks in DCM.

The standards adopted by this study have been previously used in the assessment of PerfOMs by authors of the COSMIN guidance [33]. While not originally designed for this purpose, these standards are considered to be a cornerstone in clinimetric validation and, importantly, overlap with industry guidance from the US Food and Drug Administration [17,38]. This study thus made a point to conduct and report the COSMIN Risk of Bias assessment to aid the reader in their interpretation of the rating panels (Table 2).

While construct validity testing (often criterion validity) is more commonly used by investigators, correlation coefficients require interpretation, as outlined. For similar reasons, the relative performance of instruments should not be judged solely based on the magnitude of correlation coefficients. This is reflected in clinimetric standards which instead recognize content validity as the most important arbitrator of validity and wider performance. Content validity uses stakeholder judgment and feedback to determine validity and will be further reported separately for MoveMed, following study completion. When developing and reviewing measurement instruments, understanding clinimetrics is therefore critical.

In this cohort, the impact that DCM would be expected to have on the P-mJOA and WHOQOL-Bref was similarly seen on the fast tap, hold, typing, and stand and walk MoveMed Tests. Correlations with total scores and limb-specific subscores were recorded, in accordance with prespecified expectations. The most interesting finding was the strong correlation between the P-mJOA MDUE subscore and the hold test Stability Score. This is because upper limb stability is not classically thought to be a marker of DCM. The authors attribute this finding to the composite nature of the upper limb stability construct, which includes elements of arm strength, muscle fatigue, and balance. Further studies will follow-up with more data on the subject (eg, content validity). This may very well be an example of a subclinical phenomenon that the human eye cannot catch but that mobile sensors can.

An important strength of this study is its design by individuals with formal training in clinimetrics. This is reflected in the absence of risk-of-bias factors from the COSMIN checklist in Table 2 and the study’s reporting. There is, unfortunately, a general paucity of well-designed clinimetric studies in the literature [33,34,39-41]. The use of the COSMIN manual is thus strongly encouraged by the authors. Another strength of this study was the use of PerfOMs that can collect several measurements quickly, ecologically, and longitudinally. This means that the construct should be captured more precisely, more reflective of pathology in the patient’s natural environment, and potentially more responsive to intervention. In the future, these hypotheses will be formally assessed via further clinimetric studies.

Despite its conscientious design, this study has limitations. First, standards for patient-reported methods were adapted to assess performance-based methods. This was done to overcome the absence of standardized criteria in this field and because there is precedent for it in Terwee et al [34] and the COSMIN manual [33]. Second, this study reports on 27 individuals (7 months of recruitment). The COSMIN standards are known for being rigorous (or stringent) and, ideally, at least 50 participants should be included to earn a modified Grading Of Recommendations, Assessment, Development, and Evaluations (GRADE) score of “high” [33,34,39-41]. Third, we assumed that the constructs of all WHOQOL-Bref domains would be dissimilar to the PerfOMs but this may not be the case. The WHOQOL-Bref, ultimately, contains questions on physical activity, and the relatedness of this construct to the fast tap tests and the typing tests may have been observed in Table 2. Fourth, people with a severe form of the disease may have been excluded from enrollment. This would be due to the exclusion of individuals who were unable to stand and walk without the assistance of another person. The potential risks of remote participation in this subset of individuals, however, were deemed to outweigh the benefits by the ethical committee. Further in-person research could address this limitation in the future.

Conclusions

This study provides initial evidence for the validity of the MoveMed PerfOMs in the context of adults with DCM in the community.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published paper.

Authors' Contributions

BMD and AYT conceived the study and are the guarantors. AYT, BMD, TH, and ZR collected and analyzed the data. AYT and BMD wrote the manuscript. IL, KM, ARM, ND, ZG, MK, and MRNK provided critical and independent appraisal of the methods, data, and manuscript. All authors reviewed and critically revised the manuscript prior to submission.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form and declare support from MoveMed Ltd for the submitted work. BMD is the chief executive officer of MoveMed Ltd; AYT is the chief scientific officer of MoveMed Ltd; MRNK is the chief medical officer of MoveMed Ltd; and MK is chief data officer at MoveMed Ltd. IL has received consultation fees from DePuy Synthes, Royalties, and Globus and acted as an advisor to Chiefy Inc. ARM has received research grants from AO Spine. ND is the principal investigator of a prospective degenerative cervical myelopathy study in Canada. No other relationships or activities that could appear to have influenced the submitted work.

Multimedia Appendix 1
COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) risk-of-bias checklist.
[DOCX File , 15 KB - neuro_v3i1e52832_app1.docx]

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Abbreviations

COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
DALY: disability-adjusted life year
DCM: degenerative cervical myelopathy
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
mJOA: modified Japanese Orthopaedic Association
MDLE: motor function of the lower extremities
MDUE: motor function of the upper extremities
PerfO: performance-based outcome
PerfOM: performance-based outcome measure
PRO: patient-reported outcome
PROM: patient-reported outcome measure
P-mJOA: patient-derived modified Japanese Orthopaedic Association
WHOQOL-Bref: World Health Organization Quality of Life Brief Version

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Viewpoint

Invasive Brain-Computer Interfaces: A Critical Assessment of Current Developments and Future Prospects

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Abstract

Invasive brain-computer interfaces (BCIs) are gaining attention for their transformative potential in human-machine interaction. These devices, which connect directly to the brain, could revolutionize medical therapies and augmentative technologies. This viewpoint examines recent advancements, weighs benefits against risks, and explores ethical and regulatory considerations for the future of invasive BCIs.

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KEYWORDS

brain computer interfacing; neurotechnology; brain-computer; interfacing; interface; interfaces; invasive; human-machine; human-computer; BCI; BCIs; brain-computer interface; neuroscience; technology; digital health; brain; machine learning; artificial intelligence; AI; ethics; innovation; policy; innovation; mHealth; mobile health

Perspective

Invasive brain-computer interfaces (BCIs) have recently attracted significant attention due to their potential to revolutionize the interaction between humans and machines. By directly interfacing with the brain, these devices offer profound implications for medical therapies and augmentative technologies. This viewpoint discusses the latest advancements, evaluates the benefits against the potential risks, and considers the ethical and regulatory landscapes shaping the future of invasive BCIs.

BCIs that involve invasive techniques, such as surgically implanted electrodes, are not new concepts but have seen rapid development in recent years. These devices provide a direct pathway for decoding and modulating neural activity, thereby offering unprecedented opportunities for patients with severe neurological deficits to interact with their environments in ways previously deemed unfeasible.

The progress in microfabrication technology, neural decoding algorithms, and materials science has substantially increased the capabilities of invasive BCIs. Modern electrodes can now be manufactured at scales small enough to minimize damage while maintaining high fidelity in signal recording. Techniques like endovascular BCI approaches propose minimally invasive methods to place electrodes closer to relevant neural tissues without traditional open-brain surgery [1]. Their clinical potential still has to be demonstrated.

Invasive BCIs are primarily aimed at restoring lost functions such as mobility, speech, and even cognitive faculties in patients with disabilities resulting from conditions like stroke, spinal cord injuries, and neurodegenerative diseases. For example, devices have been developed to enable individuals with paralysis to control robotic limbs or computer cursors with their thoughts alone [2,3]. Beyond therapeutic applications, there is also exploratory research into the use of BCIs for enhancing human memory and cognitive speed, suggesting a potential expansion into augmentation uses in the future [4].

The capability of BCIs to read and potentially write to the human brain raises significant ethical questions. Issues such as consent, autonomy, and the potential for influencing voluntary choices or privacy violations are of paramount concern. The privacy of neural data, akin to digital and genetic information, requires stringent safeguards to prevent unauthorized access and misuse [4-6]. To some extent, such concerns are already applicable to,

for example, deep brain stimulation devices, but BCIs will take them to the next level.

The implantation of BCI devices involves invasive procedures that carry inherent risks such as infection, inflammation, and the potential for long-term immune responses. Moreover, the permanency of these implants poses challenges in device maintenance and updates, complicating their management over a patient's lifetime [5,7]. Regulatory bodies are currently grappling with these issues, striving to develop guidelines that ensure patient safety without stifling innovation. Another area of concern is postexplantation care, in particular in research settings. For example, when study participation results in improved functioning, ethical concerns will arise when the study concludes and participation must stop.

As BCIs advance, they could significantly alter many aspects of society, from health care to employment, potentially leading to new forms of inequality. Access to and control of such powerful technologies could exacerbate social divides if not carefully managed. Public discussion and policy development must therefore keep pace with technological advancements to address these societal impacts comprehensively.

Conclusion

Invasive BCIs hold tremendous promise for transforming lives, particularly for those with severe disabilities. However, the rapid pace of development in this field necessitates careful consideration of the ethical, safety, and societal issues that accompany such transformative technologies. Balancing innovation with responsible development will be key to realizing the full potential of BCIs while minimizing potential harms.

Conflicts of Interest

PK is the editor-in-chief of *JMIR Neurotechnology* and has research lines on brain-computer interfaces that are partially funded with unrestricted research grants from Abbott Inc and Blackrock Neurotech.

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Abbreviations

BCI: brain-computer interface

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