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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 and 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.

^cNo 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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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 visuospatial 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.

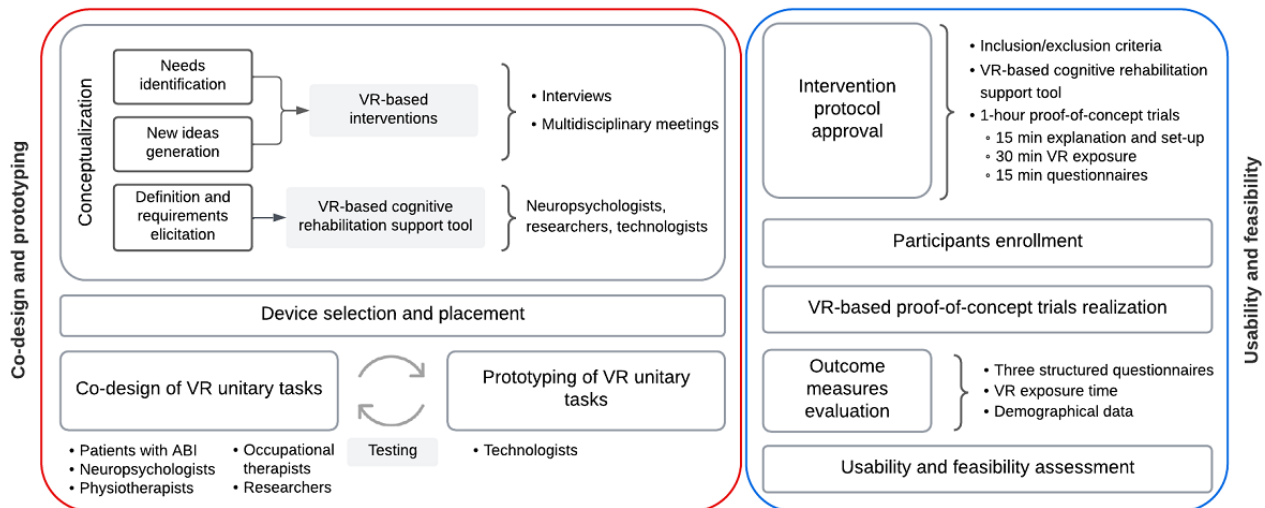
Study Design

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

^aVR: virtual reality.

^bOLED: organic light emitting diode.

^cLCD: liquid crystal display.

^dDoF: degrees of freedom.

^eIPD: 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.

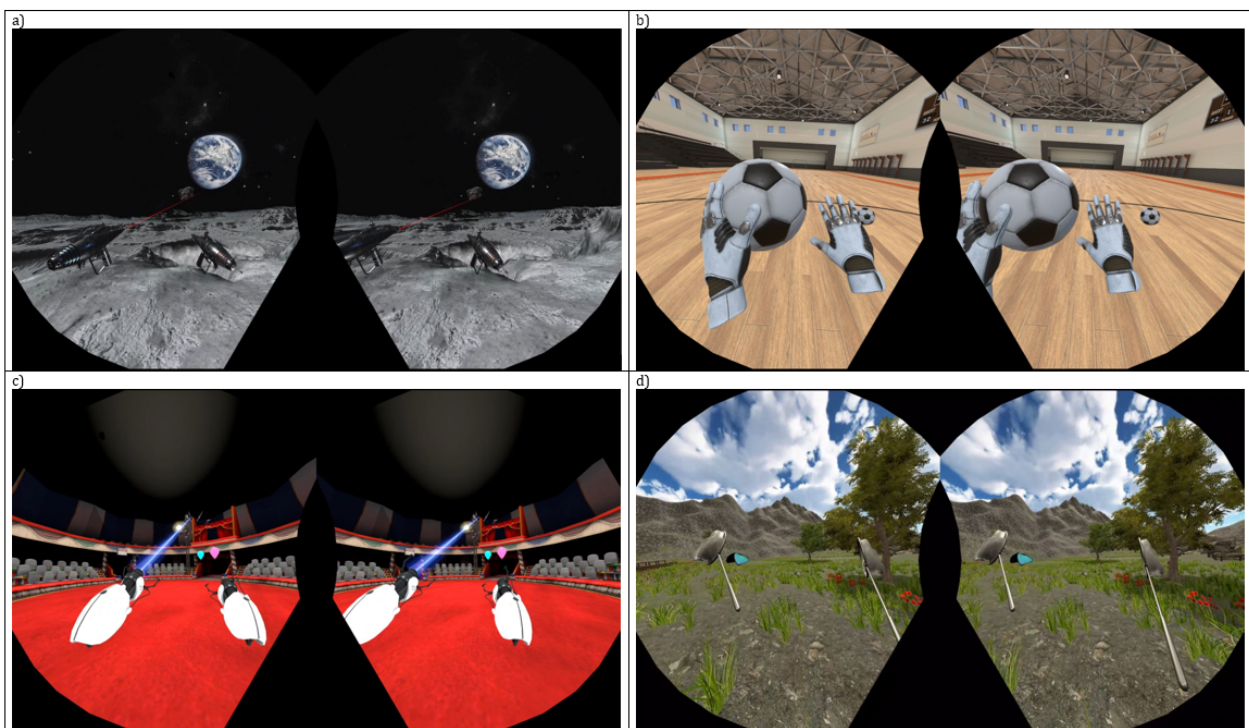
The final prototypes were attained through continuous testing and evaluations involving end users and clinical professionals. Key topics and features that underwent extensive discussion and redesign were game mechanics, interactivity, sound effects, graphic design, and variable thresholds to delineate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

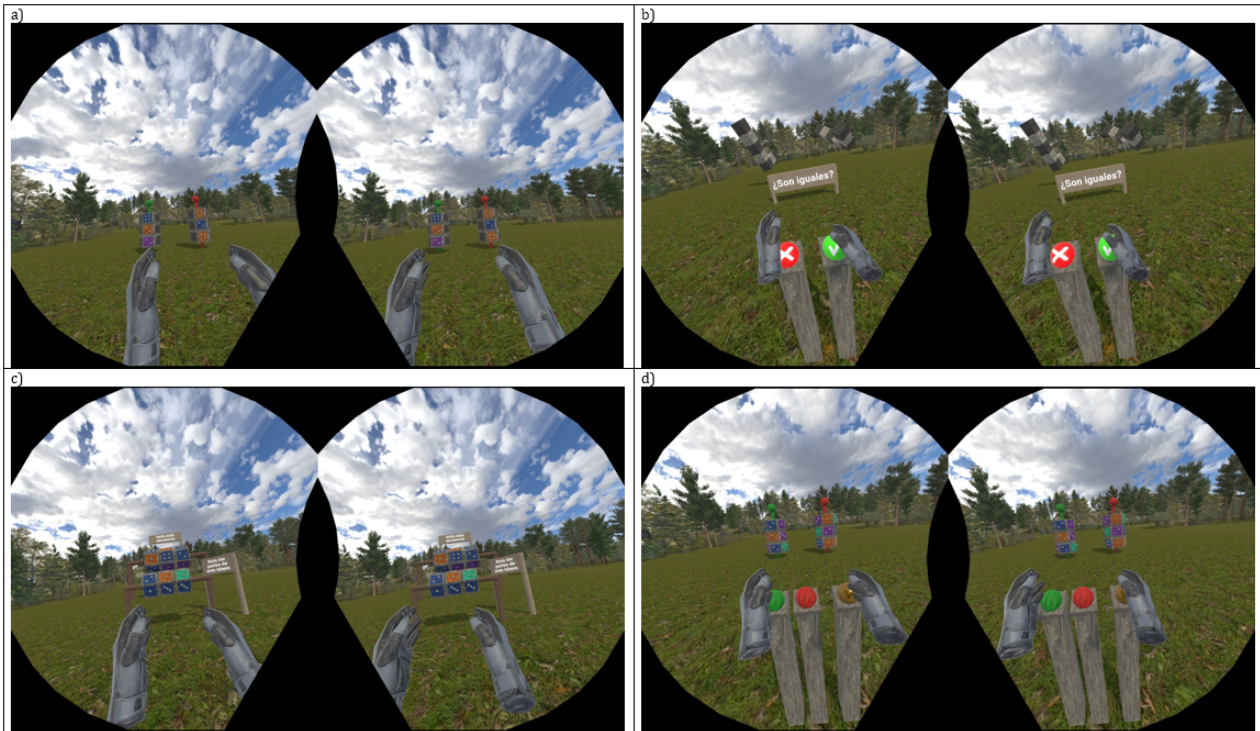
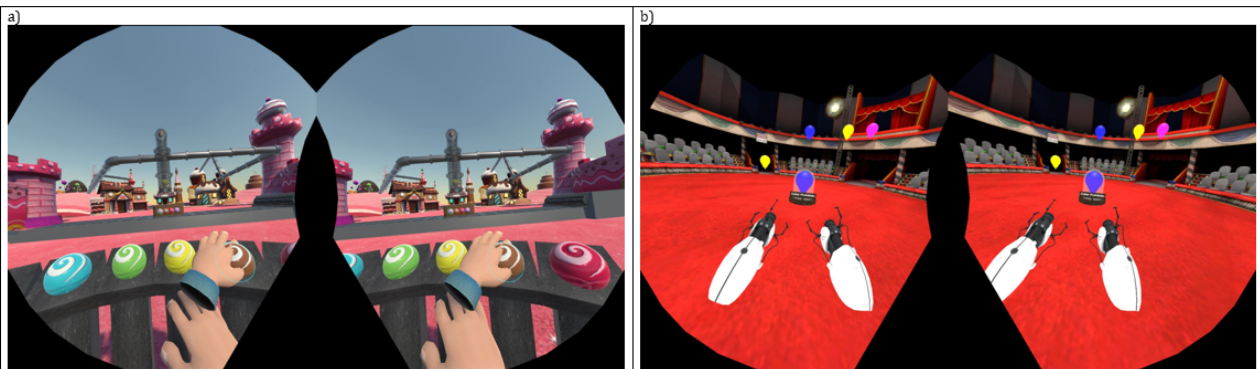


Figure 4. The 2 executive functions immersive serious games: (A) Conveyor-belt and (B) Circus-II.



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	—

^aTSI: time since injury (months).

^bNIHSS: National Institute of Health Stroke Score.

^cGCS: Glasgow Coma Scale.

^dTBI: traumatic brain injury.

^eNot 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)

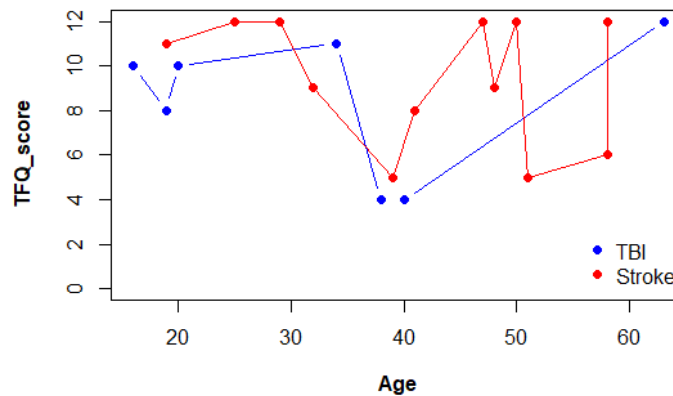
^aTSI: time since injury.

^bUQ: Usability Questionnaire.

^cTFQ: Technology Familiarity Questionnaire.

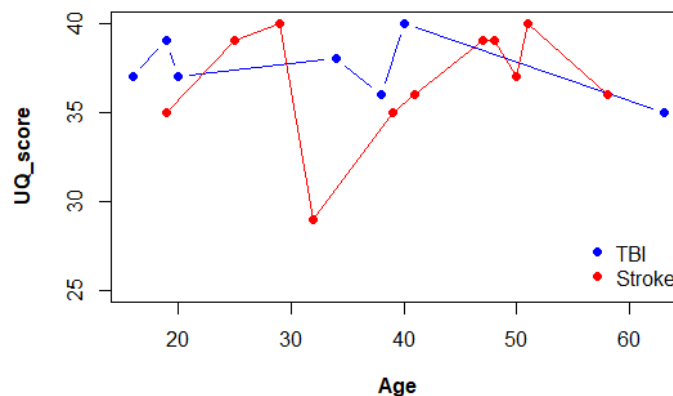
^dSSQ: Simulator Sickness Questionnaire.

^eTBI: 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.

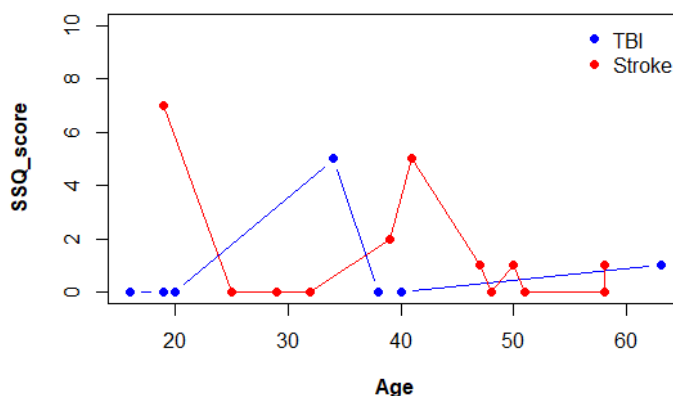
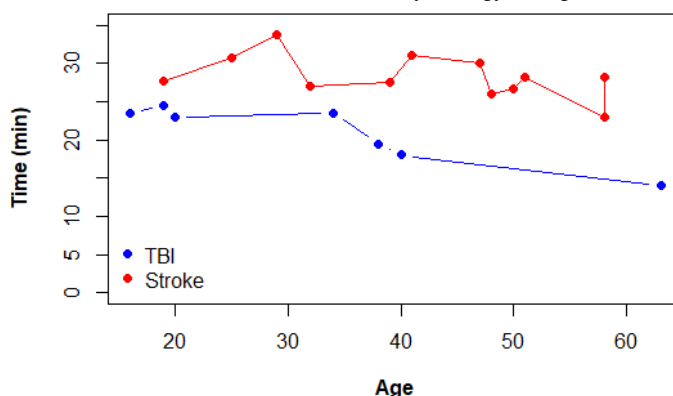


Figure 8. Comparison plot between intervention duration time differentiation by etiology and age.



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.

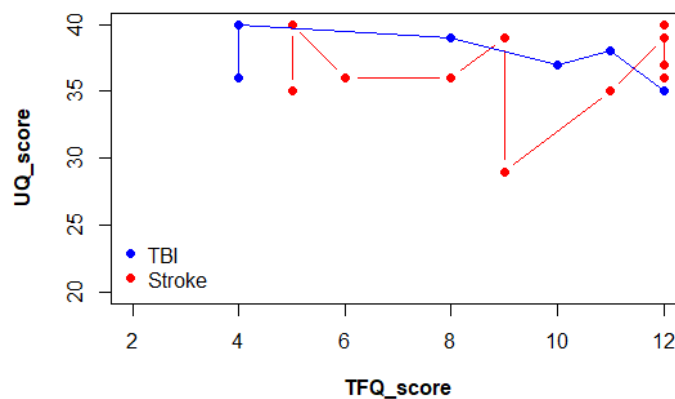
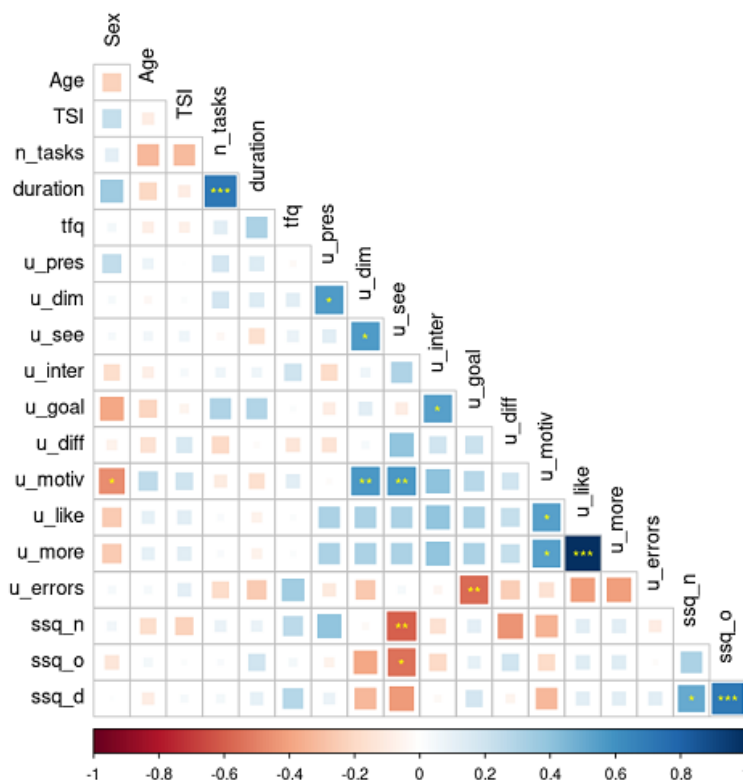


Figure 10. Correlations between sample’s demographic characteristics, number of tasks completed, session duration time, technology familiarity, usability categories, and SSQ. * $P<.05$, ** $P<.01$, and *** $P<.001$. SSQ: Simulator Sickness Questionnaire; TFQ: Technology Familiarity Questionnaire; TSI: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

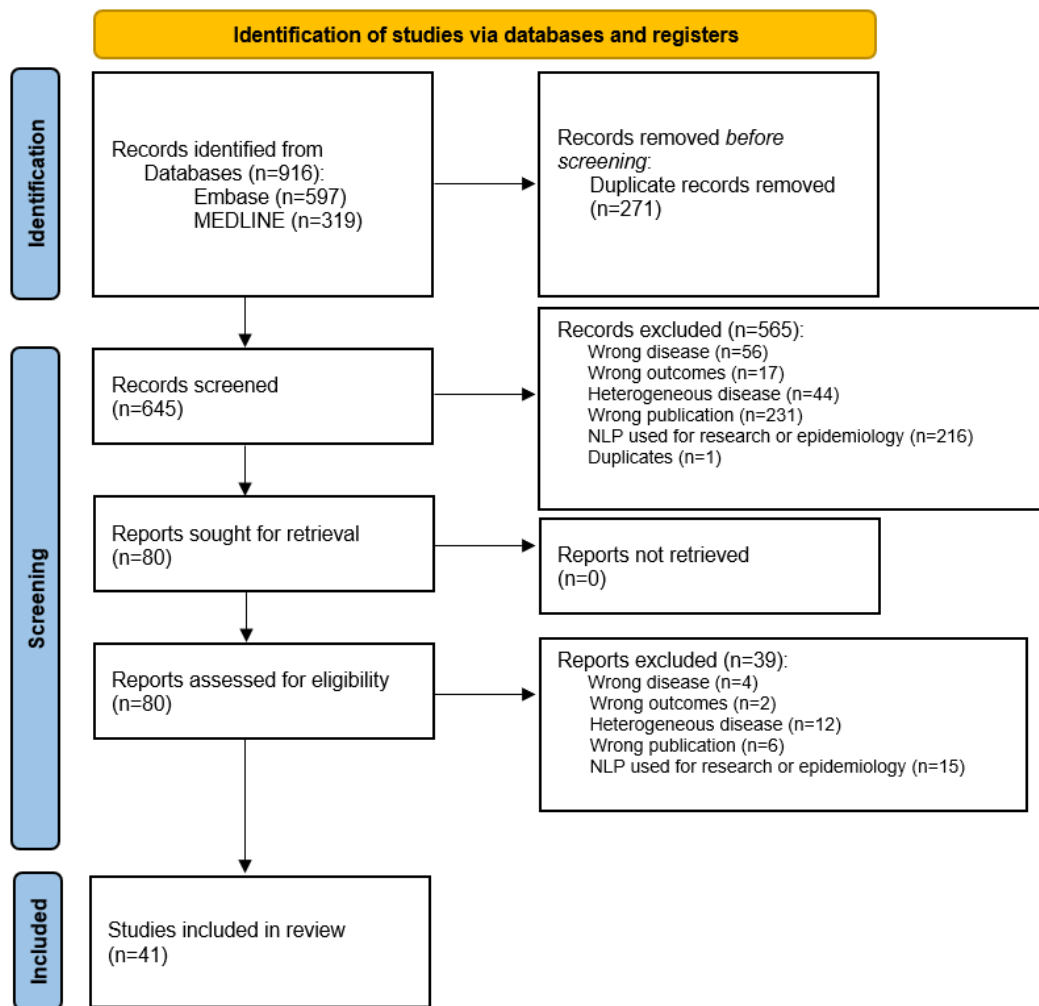


Table 1. Included studies.

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

^aNLP: natural language processing.

^bML: machine learning.

^cKNN: k-nearest neighbor.

^dMPL: multilayer perceptron.

^ePNES: psychogenic nonepileptic seizures.

^fSVM: support vector machine.

^gCNN: convolutional neural network.

^hRNN: recurrent neural network.

ⁱLSTM: long- and short-term memory network.

^jN/A: Not applicable.

^kTIA: transient ischemic attack.

^lSUDEP: sudden unexpected death in epilepsy.

^mMS: multiple sclerosis.

ⁿMMSE: Mini-Mental Status Examination.

^oICH: intracerebral hemorrhage.

^pEMR: 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)

^aNLP: natural language processing.

^bOther 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)

^aNLP: natural language processing.

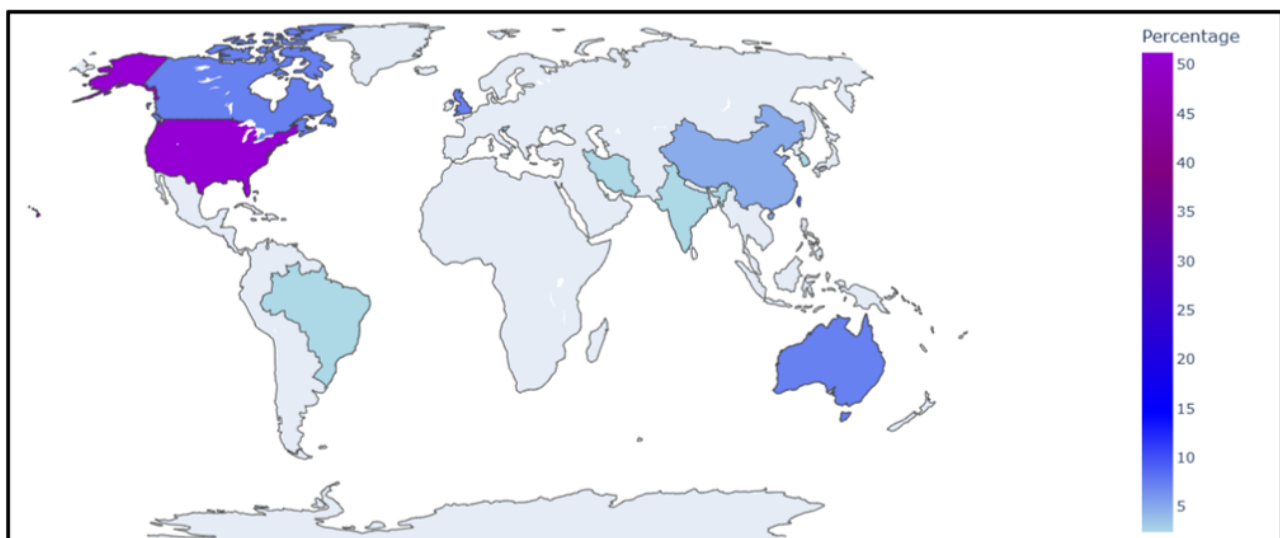
^bOther includes echocardiography reports, problem lists, and letters to referring providers.

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.

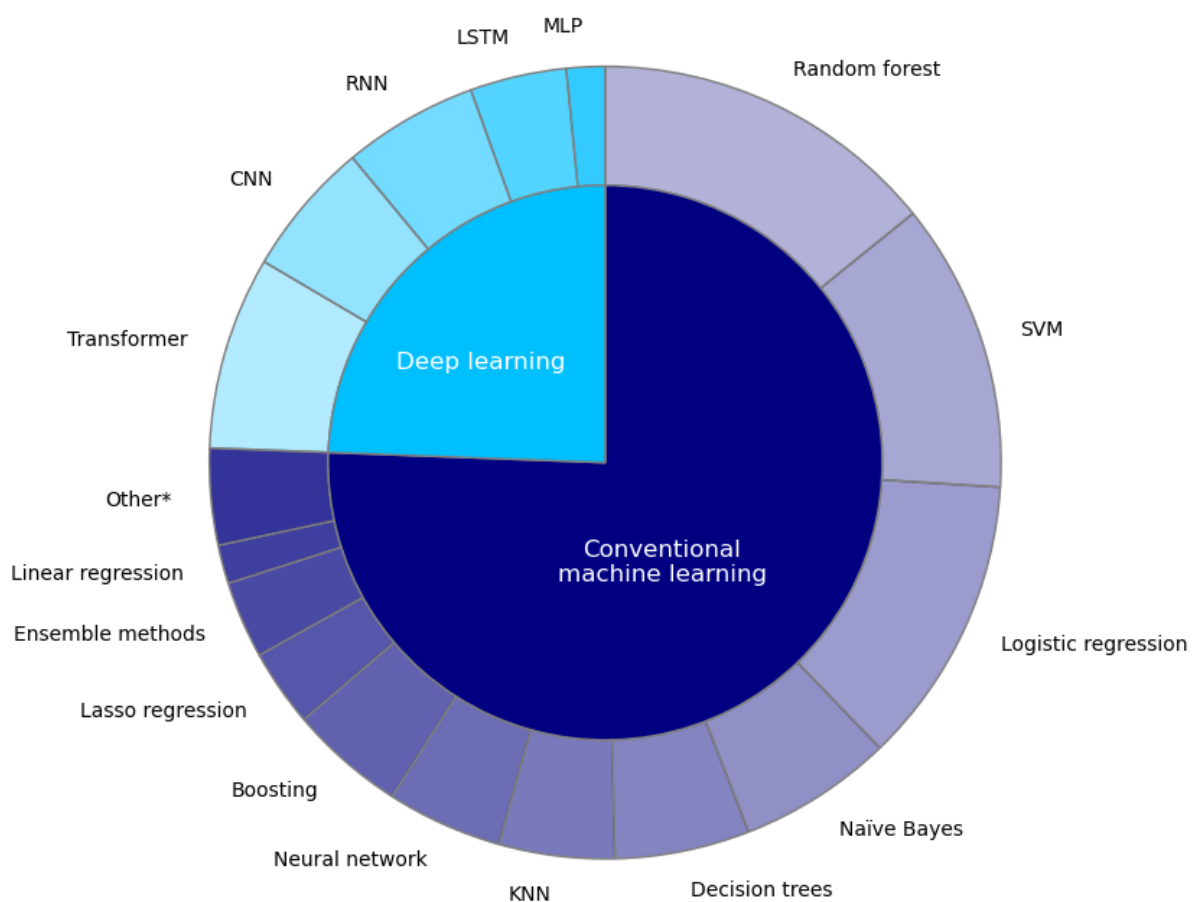
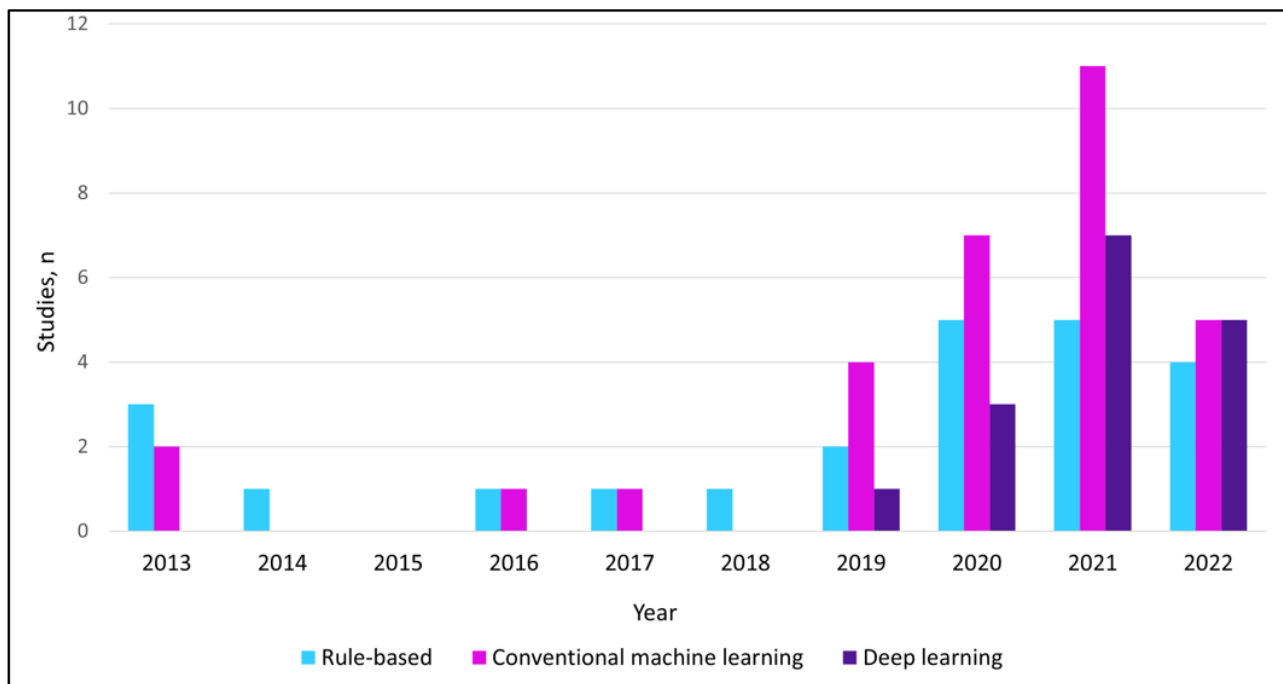


Figure 4. Number of studies applying natural language processing (NLP) to neurological conditions, stratified by NLP methodology and publication year.



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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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 (NeuroOptics). 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.

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

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.

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

^amTBI: mild traumatic brain injury.

^bGCS: Glasgow Coma Scale.

^cOne 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)	<i>P</i> 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

^aPLR: pupillary light reflex.

^bmTBI: mild traumatic brain injury.

Table 3. Best performing binary classification models^a.

Model	PLR ^b parameter combination	Accuracy, %	Sensitivity, %	Specificity, %	AUC ^c	<i>F</i> 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

^aThe 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.

^bPLR: pupillary light reflex.

^cAUC: area under the curve.

^dRF: random forest.

^eKNN: k-nearest neighbors.

^fSVM: support vector machine.

^gLR: 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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