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Viewpoint

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Transforming Perceptions: Exploring the Multifaceted Potential of Generative AI for People With Cognitive Disabilities

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Abstract

Background: The emergence of generative artificial intelligence (GenAI) presents unprecedented opportunities to redefine conceptions of personhood and cognitive disability, potentially enhancing the inclusion and participation of individuals with cognitive disabilities in society.

Objective: We aim to explore the transformative potential of GenAI in reshaping perceptions of cognitive disability, dismantling societal barriers, and promoting social participation for individuals with cognitive disabilities.

Methods: This study is a critical review of current literature in disability studies, artificial intelligence (AI) ethics, and computer science, integrating insights from disability theories and the philosophy of technology. The analysis focused on 2 key aspects: GenAI as a social mirror reflecting societal values and biases, and GenAI as a cognitive partner for individuals with cognitive disabilities.

Results: This paper proposes a theoretical framework for understanding the impact of GenAI on perceptions of cognitive disability. It introduces the concepts of GenAI as a "social mirror" that reflects and potentially amplifies societal biases and as a "cognitive copilot" providing personalized assistance in daily tasks, social interactions, and environmental navigation. This paper also presents a novel protocol for developing AI systems tailored to the needs of individuals with cognitive disabilities, emphasizing user involvement, ethical considerations, and the need to address both the opportunities and challenges posed by GenAI.

Conclusions: Although GenAI has great potential for promoting the inclusion and empowerment of individuals with cognitive disabilities, realizing this potential requires a change in societal attitudes and development practices. This paper calls for interdisciplinary collaboration and close partnership with the disability community in the development and implementation of GenAI technologies. Realizing the potential of GenAI for promoting the inclusion and empowerment of individuals with cognitive disabilities requires a multifaceted approach. This involves a shift in societal attitudes, inclusive AI development practices that prioritize the needs and perspectives of the disability community, and ongoing interdisciplinary collaboration. This paper emphasizes the importance of proceeding with caution, recognizing the ethical complexities and potential risks alongside the transformative possibilities of GenAI technology.

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KEYWORDS

generative artificial intelligence; cognitive disability; social participation; AI ethics; assistive technology; cognitive disorder; societal barriers; social inclusion; disability study; social mirror; cognitive partner; empowerment; user involvement; GenAI; artificial intelligence; neurotechnology; neuroinformatics; digital health; health informatics; neuroscience; mental health; computer science; machine learning

Introduction

In the era of generative artificial intelligence (GenAI), traditional notions of personhood and normality are being challenged [1-4]. Technological advances are blurring the boundaries between human and machine capabilities, offering an opportunity to expand the limits of social inclusion and promote change in attitudes toward people with disabilities [1]. As artificial intelligence (AI) systems demonstrate increasingly sophisticated cognitive abilities, they prompt us to reconsider what qualities define personhood and human intelligence. This paper examines the potential of GenAI to disrupt limiting conceptions of morality and humanity, focusing on the implications of GenAI for the social status of people with cognitive disabilities. This paper also proposes a practical toolkit for GenAI development and engineering professionals—product managers, data scientists, and developers—to help incorporate these insights into their work.

Cognitive disability refers to a wide range of impairments affecting cognitive functions such as learning, problem-solving, judgment, communication, and social interaction [5]. Examples of cognitive disabilities include intellectual disability, attention-deficit/hyperactivity disorder, autism spectrum disorders, specific learning disabilities (such as dyslexia), and brain injuries (such as traumatic brain injury or stroke) [5-7]. It is important to emphasize the variety of individuals with cognitive disabilities, each one possessing a unique combination of strengths, impairments, and potential, which means that cognitive disabilities require personalized approaches to intervention. While recognizing the diverse nature of cognitive disabilities and the need for tailored solutions, this paper focuses on the general potential of GenAI to improve the lives of people across the spectrum of cognitive disabilities.

Engaging with the integration of GenAI and individuals with cognitive disabilities is a new direction in the use of technology in the field of disability. The potential for AI to support and empower this population lies in its ability to perform cognitive tasks such as reasoning, planning, decision-making, and communication—areas that are challenging for people with cognitive disabilities [8-10]. The ability of AI to remove barriers and open new paths for inclusive and equitable participation makes it especially relevant for this population [11]. An in-depth analysis of this ability requires examining the philosophical and ethical implications of AI for conceptions of humanity and morality, questions that directly determine how society views and accommodates individuals with cognitive disabilities. These are fundamental inquiries into the nature of intelligence, personhood, consciousness, and human agency, which largely determine the degree of participation and inclusion for this group.

Personhood and AI: An Opportunity for Paradigm Shift

The concept of personhood, which emerged as a central topic in bioethical debates surrounding topics such as abortion, stem cell research, and euthanasia, has evolved into a complex and multifaceted construct that now spans multiple disciplines [12]. Inherently normative in nature, personhood involves value judgments and ethical considerations regarding how we ought to treat and perceive others rather than merely describing observable facts. Personhood is not rooted exclusively in our biology and experiences but in our essence and identity. This identity, however, is not formed in isolation; it is dynamically shaped in an intricate interaction between self-perception and the perception of others and interaction with them. Rosfort [13] argued that this conceptualization of personhood reveals its profoundly relational and social nature, demonstrating how identity and perception of self-worth are inextricably woven into interactions and the broader human context.

The concept of “personhood” has long served as a central criterion in bioethical discussions, determining which entities deserve moral consideration and rights [3]. As a result, this notion has also functioned as a mechanism of exclusion, denying basic rights and opportunities to those deemed cognitively “abnormal” [14].

For example, historically, people with cognitive disabilities were excluded from the public sphere and denied the right to make decisions for themselves [15,16]. Even today, despite significant progress in discourse and work based on the “social model” (an approach that views disability as created by societal barriers rather than by individual impairments alone) [17] and the “minority group model” (which recognizes people with disabilities as a marginalized minority group) [18], exclusion still exists in various aspects of life. People with cognitive disabilities still face barriers to accessing higher education and vocational training because of preconceived notions about their abilities [19]. Despite relevant skills, they have difficulties securing meaningful employment and career advancement opportunities because of social stigma and prejudice [20]. Participation in political or civic decision-making processes, such as voting or community involvement, is limited by discriminatory perceptions of the competence of individuals with cognitive disabilities [21]. They are also excluded from leisure, social, and cultural activities because of a lack of access or restrictive attitudes toward their participation [22].

These exclusion examples illustrate how, as a result of conceptualizing what constitutes a person of merit, individuals with cognitive disabilities are often excluded in the deepest and broadest ways from society. This mechanism is difficult to identify because it operates through our language and the most basic organized mechanisms of any society: law, health care system, education system, and more [23].

Breaking entrenched concepts and perceptions of personhood is challenging because they are deeply embedded in societal structures and norms, but emerging technologies are beginning to challenge these long held beliefs. GenAI offers an opportunity to challenge the definition of personhood perceptions by demonstrating skills previously considered unique to humans [1,4]. Although these capabilities are not yet perfect in AI, their very existence challenges the idea that such traits belong exclusively to the “normal” cognitive function of humans and that social participation is conditional on the presence of these abilities.

The revolutionary potential of GenAI invites us to reexamine the criteria for membership in the moral community and expand them beyond limiting standards. Instead of relying on a narrow model of "correct" cognitive abilities as a prerequisite for rights and participation in society [14], we may adopt, with the assistance of GenAI, a more inclusive view that recognizes human diversity and the inherent value of all individuals, regardless of their abilities [24]. By showcasing the potential of machines to exhibit complex cognitive traits, GenAI challenges the notion that certain abilities are essential for personhood and moral status. It initiates a discourse on the need to redefine our understanding of what it means to be human and to have moral worth, moving away from a focus on cognitive benchmarks and toward a more encompassing vision of human dignity and rights [1,4].

Although AI presents opportunities to challenge our understanding of personhood, there are legitimate concerns about its potential to exacerbate exclusion and narrow definitions of "normal" human cognition. The inherent biases in AI systems, stemming from their training data and algorithmic design [25-28], risk reinforcing and amplifying existing societal prejudices [29]. As AI increasingly influences decision-making processes in areas such as employment, health care, and criminal justice, there is a danger that it could lead to more stringent and narrow criteria for what constitutes "normal" human functioning. This could inadvertently heighten barriers for individuals with cognitive differences, further marginalizing them from full societal participation [30]. Moreover, as AI systems become more sophisticated in mimicking certain human cognitive abilities, there is a risk that societal expectations of human performance might be unrealistically elevated, potentially creating an even more exclusionary standard of "normal" [31]. Thus, while AI challenges our notions of personhood, it simultaneously risks entrenching and exacerbating existing forms of exclusion, highlighting the critical need for ethical AI development and deployment considering diverse human experiences and capabilities. In the following sections, we will explore 2 key areas where GenAI has the potential to drive significant change: GenAI as a social mirror and GenAI as a cognitive partner. These 2 domains highlight the multifaceted impact that GenAI can have on reshaping perceptions, removing barriers, and promoting participation of individuals with cognitive disabilities on the one hand, and exacerbating existing biases and exclusions in society on the other.

Generative AI as a Social Mirror: Opportunity and Challenge

Overview

Vallor's [32] conceptualization of AI as a societal mirror provides a compelling framework for understanding the role of AI in reflecting and potentially amplifying societal biases, particularly concerning cognitive disabilities. This mirror metaphor can be understood as follows: just as a physical mirror reflects the image of what stands before it, AI systems reflect the data, values, and biases present in the society that created them. However, unlike a simple reflection, AI systems can amplify and distort these reflections, much as a funhouse mirror might exaggerate certain features.

This mirror effect illuminates how AI systems, trained on biased data, risk perpetuating existing prejudices against individuals with cognitive differences. AI essentially learns from and then projects back the biases inherent in its training data, potentially reinforcing and spreading these biases further. Paradoxically, this same reflective quality presents a unique opportunity to identify and address longstanding societal biases, rendering implicit prejudices explicit and subject to scrutiny. By closely examining what the AI "reflects back" to us, we can gain insights into biases that might otherwise remain hidden or unacknowledged in society.

Vallor [32] posits that AI systems in general, and GenAI systems in particular, are not merely neutral technological tools but mirrors reflecting the values, norms, and biases prevalent in human society. Given that these systems are constructed upon data and content created by humans, they inherently risk replicating and perpetuating prejudices and discrimination against marginalized groups, including people with cognitive disabilities [27,33].

A study by Gadiraju et al [34] demonstrated this mirroring effect in action. They conducted 19 focus groups with 56 participants with various disabilities who interacted with a dialog model based on a large language model. The researchers found that the model frequently perpetuated harmful stereotypes and narratives about disability. For example, the model often fixated on physical disabilities, particularly wheelchairs, while neglecting other types of disabilities. It also tended to portray people with disabilities as passive, sad, and lonely, reinforcing the misconception that disability is inherently negative. Additionally, the model sometimes produced what participants referred to as "inspiration porn," objectifying people with disabilities as sources of inspiration for nondisabled people.

For example, if the information used to train AI systems contains stereotypical or derogatory expressions toward people with cognitive disabilities, there is a significant risk that these systems might "learn" to adopt discriminatory attitudes. The potential consequences are severe: AI systems could rank individuals with cognitive disabilities as having lower potential in employment or educational contexts, limit their access to certain services, or make biased decisions about them in critical areas such as insurance or credit [35].

When we look into the societal mirror reflected by AI, several possible human responses can be identified. One metaphorical response is "breaking the mirror," representing human resistance to AI use and the insights it presents [36]. While this approach attempts to avoid the uncomfortable truths AI exposes, it risks missing out on the potential benefits and insights AI can offer. Another metaphorical strategy is "cleaning the mirror," where humans attempt to eliminate biases through AI alignment processes [37]. This approach aims to create AI systems aligned with human values and intentions, striving for a bias-free environment. However, it risks producing an artificially sterile system that fails to reflect the complexities of human cognition and interaction, potentially making AI less relevant and less capable of addressing real-world complexities.

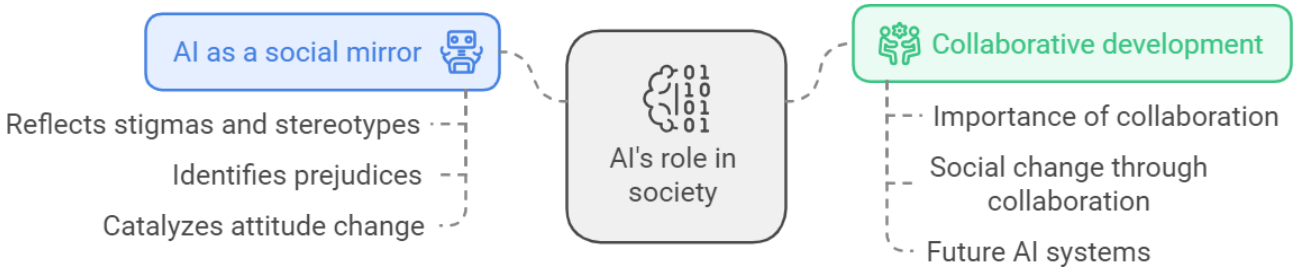
The third and most promising approach involves using reflection as a call to action in the real world. This method requires humans to acknowledge the biases reflected by AI and use this awareness as a catalyst for societal change. It demands active engagement and concrete actions from us as humans to address these issues, both in our AI systems and in society at large [38]. This approach recognizes that if such action is taken, over time, the reflection in the AI mirror itself can change, not as a result of erasing biases in the machine as in the second option, but as a consequence of real societal change that is then differently reflected in the AI mirror.

To implement this approach specifically within the realm of AI development and deployment, we must adopt advanced techniques and ensure inclusive human involvement. As contemporary AI systems increasingly incorporate vast datasets populated from the internet, traditional methods of addressing biases through direct data manipulation, such as the "datasheets" approach proposed by Gebru et al [39], while still valuable in certain contexts, have become more challenging to implement comprehensively. This shift has led to the adoption of complementary techniques that can handle the scale and complexity of modern AI systems such as self-supervised learning [40] and reward modeling [41]. Crucially, these techniques still require human decision-making at key junctures.

To truly address biases and create more equitable AI systems, particularly regarding cognitive disabilities, we must ensure that people with cognitive disabilities are actively involved in these decision-making processes. This collaborative approach aligns with our third strategy, emphasizing real-world action and societal change. By critically examining the biases revealed in AI outputs and involving diverse perspectives in the development process, we can work toward creating more inclusive AI systems. This approach not only helps in developing fairer algorithms and more representative models but also contributes to broader societal change [1,4]. In this way, the AI mirror becomes not just a reflection of our current culture, but a catalyst for the more inclusive society we aspire to create [16,42].

In conclusion, as illustrated in Figure 1, GenAI has the potential to promote social justice and shift perceptions regarding cognitive disabilities. To harness this potential, collaborative work and ongoing effort are required to embed values of accessibility, inclusion, and respect for diversity at the core of technological development. These steps can transform the "reflection in the mirror" into a positive and inclusive image for people with cognitive disabilities, potentially leading to broader societal changes in perception and inclusion.

Figure 1. GenAI as a social mirror: collaborative development for societal change. AI: artificial intelligence; GenAI: generative artificial intelligence.



While this mirror metaphor provides valuable insights, it is important to recognize its limitations. Vallor's conceptualization, though powerful, doesn't fully capture the multifaceted potential of AI, particularly for people with disabilities. It overlooks its capability to actively solve previously intractable problems and enhance accessibility. To provide a more comprehensive understanding, we must expand our view beyond the perception of AI as a mere reflective tool. In the following section, we propose considering AI not only as a mirror but also as a cognitive partner for people with disabilities, emphasizing its potential to actively support and empower individuals with cognitive differences in navigating the world.

Generative AI as a Cognitive Partner for People With Disabilities

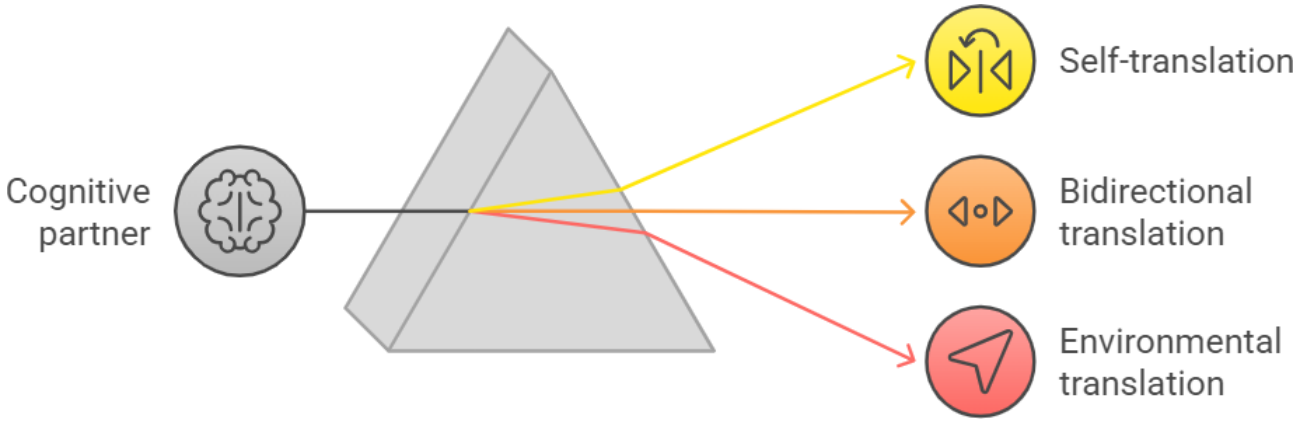
Beyond Vallor's mirror metaphor for AI and its contingent inference on social change for people with cognitive disabilities, a significant potential of GenAI lies in its ability to serve as a "cognitive partner," empowering participation of these people in life domains that were previously blocked or limited for them [43-45]. This partnership can be metaphorically described as a "cognitive copilot" (an AI assistant for complex cognitive tasks), assisting and empowering the individual with tasks requiring complex cognitive functions. For example, GenAI can help a person with cognitive disabilities manage daily tasks such as scheduling, budgeting, or navigating urban spaces by providing personalized reminders, recommendations, and guidance [46,47]. Additionally, it can serve as an advisor in complex social situations, such as interpreting body language [48], suggesting appropriate responses to expressions of anger or mockery from others, or assisting in decision-making [1,49]. In this way, GenAI may act as a kind of "social copilot," providing real-time support and feedback, allowing persons with cognitive disability to expand their circle of social interactions, inclusion, and activities.

One of the outstanding strengths of GenAI is its ability to function as a translator and mediator between languages, concepts, and realities. For people with cognitive disabilities, translation and mediation pose a central challenge in daily life, both in understanding the environment and in expressing themselves in a way others can understand [50]. With its natural learning and processing capabilities, GenAI can bridge these gaps and make information and communication more accessible.

The application of GenAI as a cognitive copilot can focus on 3 main areas (Figure 2):

1. Translating and making the inner world of people with cognitive disability accessible to themselves: GenAI can help people with cognitive disabilities better understand themselves, their thoughts, emotions, and needs. This is achieved by providing explanations and conceptualizations in clear and accessible language, identifying and interpreting emotional states, and suggesting strategies for coping with challenges [50]. GenAI can serve as an "internal translator" that through a process of assistive conceptual scaffolding and cognitive structuring [51] assists individuals in accurate self-understanding and self-expression.
2. Bidirectional translation and mediation in interpersonal communication: By analyzing interpersonal and social information, GenAI can mediate interactions with other people, making it possible to negotiate the complexities inherent in human communication more successfully. The unique contribution of GenAI in this area lies in its ability to bridge the communication gap in both directions, helping the person with cognitive disability understand the social environment, the intentions of others, and the implicit messages in discourse, and making the person's wants, needs, and emotions more accessible to the social environment [1]. For example, on one hand, GenAI can offer interpretations of social cues and recommend appropriate responses, and on the other assist individuals in articulating their thoughts more clearly and presenting their unique perspectives. The technology can serve as a "two-way social translator," enabling people with disability and their environment to better understand each other and promote respectful and equitable communication.
3. Making the physical environment and public spaces accessible: GenAI can act as an "environmental translator," converting complex information about the world into a clear and disability-friendly format. This can include, for example, simplifying official texts, graphically converting numeric data, or creating interactive guides for navigating public spaces [52]. Thus, GenAI models that are open to the public can "see" and "understand" photos and videos and describe their content [1], so that people with cognitive disabilities may gain greater access and independence in managing their lives.

Figure 2. Three main areas of GenAI application as a cognitive partner. GenAI: generative artificial intelligence.



The goal is not to "normalize" individuals with cognitive disabilities or to erase their disability. The cognitive partner metaphor, similar to Vallor's mirror metaphor, can show how the use of AI might exacerbate exclusionary attitudes and further marginalize individuals with disabilities. Therefore, using AI for social change in our attitude toward people with cognitive disabilities means that the aim of this technology should be to enable access to environments and spaces that were previously closed or socially inaccessible to them, while also facilitating the accessibility of these environments to the individuals themselves. The approach should be person-centered, respecting diversity, and tailored to the unique aspirations and needs of everyone, rather than imposing a uniform standard of "proper" functioning.

Serious consideration must be given to the ethical implications of such a close integration between humans and machines, particularly in the areas of autonomy and responsibility. Questions of privacy, data security, and people's ownership of decisions made by AI systems need to be thoroughly examined [52,53]. Robust oversight and regulatory mechanisms must be in place to ensure the responsible and ethical use of AI, safeguarding the rights and well-being of users. This is especially critical when working with vulnerable populations such as people with cognitive disabilities, where protecting individual autonomy is important [27,33].

In conclusion, although AI-based "cognitive copilot" applications for people with cognitive disabilities have the potential to remove barriers, increase participation, and promote equal opportunities across various domains of life, it is essential to proceed with caution. This technology must function as a "translator" to contribute to a more inclusive and equitable society, and we must remain vigilant to its risks. Ensuring that AI development is person-centered, ethically sound, and involves active participation from the disability community is crucial for harnessing its benefits without worsening existing biases and systemic barriers.

Implication for AI Developers and Technologists

GenAI has immense potential to promote inclusion and equality for people with cognitive disabilities but to realize this potential requires a perceptual shift on the part of developers, engineers, researchers, and product managers. Instead of focusing narrowly on "fixing" certain impairments, they must adopt a more holistic approach that views technology as a lever for social integration

and broad improvement in quality of life [54-56]. This involves a transition from regarding GenAI as a mere technical solution to perceiving it as a tool for effecting social change for the population with cognitive disabilities.

In practice, close and ongoing collaboration with people with cognitive disabilities throughout all stages of development is important [57]. Development teams must learn from the unique experiences and needs of individuals with cognitive disability and meaningfully integrate them into the design and construction of GenAI systems and prompts.

Recent research has demonstrated the feasibility and importance of this approach. For example, Newbutt et al [58] conducted a systematic review of studies involving autistic individuals in the design of extended reality technologies. They found that out of 20 studies published between 2002 - 2022, several successfully engaged autistic individuals as active co-designers and cocreators, allowing them to shape the final products according to their needs and preferences. This highlights the growing trend and importance of including the target users in the design process.

This requires a joint definition of goals, adapting user interfaces and user experience to their modes of thinking and communication, and clearly formulating principles of cognitive accessibility from the earliest planning stages [59]. The aspiration is for the empowerment and inclusion of people with cognitive disabilities to be embedded in the core of the technology and in the layer of its use.

Bircanin et al [60] presented a practical approach to including adults with severe intellectual disabilities in co-design through active support. They demonstrated how principles such as “every moment has potential,” “graded assistance,” “little and often,” and “maximizing choice and control” can be applied in design contexts to ensure meaningful participation of individuals with severe cognitive disabilities. This approach provides concrete strategies for AI developers to engage with this population during the development process.

For example, it is important to examine how the prompt-based user interface can be made accessible and adapted to the cognitive and communication characteristics of people with different types of cognitive disabilities. Consideration should be given to whether the development of dedicated products is the right direction or whether personal adaptation at the level of the individual user is preferable [61]. Answering such questions requires ongoing discourse and feedback from the community itself.

Dirks [57] explored the ethical challenges in inclusive software development projects with people with cognitive disabilities. The study emphasized the importance of maximizing choice and control for participants, using a graded assistance approach, and ensuring every moment has potential for meaningful engagement. These principles can guide AI developers in creating more inclusive design processes.

To assist developers and researchers in implementing the principles presented in this paper, we propose a working protocol specifically tailored to the development challenges of GenAI technologies aimed at people with cognitive disabilities. The protocol (Table 1) is based on the model developed by Amershi et al [62], which was formulated following comprehensive research, including a review of academic and industry literature, interviews with experts, and an examination of a wide range of AI-based products. The original model defines 18 general guidelines for designing human-AI interactions across different time frames and stages of interaction. In practice, these guidelines serve as a framework for developing human-centered AI systems, focusing on aspects such as transparency, fairness, reliability, safety, privacy, security, and accountability. Developers and designers use these guidelines to enhance human-AI interaction by implementing practices such as explaining AI decisions to users, designing interfaces that enable user control and feedback, and incorporating mechanisms to identify and mitigate biases [63].

Table . Protocol for designing artifical intelligence (AI) interactions for people with cognitive disabilities.[a]

Stage and dimension		Guidelines for AI interaction with people with cognitive disabilities	Implementation examples
Initial			
	Personal	I1. Identify and adapt to the user's unique cognitive and emotional needs.	I1. Create a personal profile including preferences, abilities, and challenges.
	Interpersonal	I2. Show awareness of the social and cultural context of system use.	I2. Consider the human environment (eg, caregivers or family members) as part of system definition.
During interaction			
	Personal	D1. Provide custom-tailored, gradual, and structured responses to personal needs during use.	D1. Identify difficulties and adapt the level of assistance and feedback in real time.
	Interpersonal	D2. Promote positive and reciprocal communication with the human environment.	D2. Mediate social interactions by simplifying and explaining social cues.
	Environmental	D3. Assist in orientation, navigation, and independent functioning in complex spaces.	D3. Provide detailed instructions and cues on proper conduct in different places.
When the system errs			
	Personal	E1. Handle errors respectfully and in an empowering way, with emphasis on learning and progress.	E1. Provide repeated opportunities to try again, together with verbal encouragement.
	Interpersonal	E2. Involve support persons in the process of learning and correction.	E2. Provide a possibility for a caregiver to assist in problem-solving or making necessary adjustments.
	Environmental	E3. Avoid placing responsibility on the user in complex or unexpected situations.	E3. Make human backup available by default in case of significant problems.
Over time			
	Personal	T1. Continually adapt to the pace of development, learning, and changes in personal needs.	T1. Track progress and adapt tasks and goals accordingly.
	Interpersonal	T2. Show sensitivity to changes in relationships and roles within the support circle.	T2. Update user profiles and access settings based on feedback from the environment.
	Environmental	T3. Show flexibility and adaptability to changing environments and transitions between contexts.	T3. Automatically detect location changes and provide relevant recommendations.
	Collaboration	T4. Actively involve users and stakeholders in the ongoing development of the system.	T4. Provide mechanisms for receiving feedback and involving users in decisions about updates and improvements.

[a]The model for this protocol by Amershi et al [62] is based on extensive research and analysis of a range of artificial intelligence products and defines 18 general guidelines across different stages of interaction. We adapted and extended this model to address specifically the needs and challenges of designing artificial intelligence technologies for people with cognitive disabilities. The protocol incorporates 4 key dimensions: personal, interpersonal, environmental, and collaborative, and provides concrete examples of how these considerations can be integrated throughout the life cycle of the artificial intelligence system. By implementing this protocol, developers can create artificial intelligence tools that empower and enhance the lives of individuals with cognitive disabilities.

Building on the analysis presented in this paper, we expand the model of Amershi et al [62] and adapt it to the 4 central dimensions in which AI systems can assist people with cognitive disabilities: the personal, the interpersonal, the environmental, and the collaborative. For each of these dimensions, we propose guidelines and offer practical examples of how the relevant considerations can be embedded at different stages of the system life cycle, from defining the initial requirements, through ongoing interaction, to continuous adaptation and improvement. The proposed protocol serves as a foundation that requires further development, testing, and investigation, but it can serve as a starting point for discourse and the advancement of best

practices in designing AI systems for individuals with cognitive disabilities.

Conclusion

The emergence of GenAI technologies represents a pivotal moment in reconceptualizing disability and personhood. We suggest that the advent of GenAI challenges assumptions about what qualifies an individual as a "person" and questions the notion that cognitive abilities are the sole determinant of one's rights and societal participation.

In this paper, we explored the transformative potential of GenAI in reshaping perceptions, dismantling barriers, and empowering individuals with cognitive disabilities. By serving as a social mirror [32], AI systems can expose and challenge deeply ingrained biases and prejudices, compelling us to confront the ways we have historically marginalized and excluded the population with cognitive disabilities. Simultaneously, by functioning as a cognitive partner, GenAI may provide unprecedented opportunities for individuals with cognitive disabilities to participate in society.

Realizing this vision requires more than technological innovation, however. It demands a gradual shift in societal attitudes and a sincere effort to involve people with cognitive disabilities in the AI development process, granting them autonomy and recognizing and valuing their abilities. This is where the role of technology professionals and GenAI developers becomes crucial.

The importance of designing AI thoughtfully lies in the understanding that whether we consider AI as a mirror or as a cognitive partner, both metaphors indicate that AI will increasingly mediate how we perceive the world, ourselves, and others, confirming once again McLuhan's [64] statement that "the medium is the message." This means that the significant effect of AI lies not merely in the content we explore through it but in how its very use changes us. Therefore, the design and development of AI tools will profoundly influence the future of human society, how we perceive individuals with disabilities, as well as the rights and social positions they will attain. Therefore, how AI is being shaped now will determine its role in reinforcing existing biases or promoting a more inclusive and equitable society.

The proposed protocol, based on the work by Amershi et al [62], offers a practical framework for implementing these principles as part of GenAI development for people with cognitive disabilities. This paper marks only the beginning of the discussion about GenAI and developmental disabilities, therefore we must remain vigilant regarding the ethical and social implications of GenAI and continue to engage in open, multidisciplinary dialogue about how to harness its potential for the greater good.

The path ahead is complex and challenging, but it is also filled with immense possibilities. As we look toward the future, the evolution of AI from reactive, prompt-based systems to proactive, autopilot models promises to further expand these possibilities, particularly for individuals with cognitive disabilities. These advanced systems, capable of learning user needs and initiating interactions without explicit prompts, could provide more seamless and intuitive support, potentially revolutionizing the way we approach cognitive assistance.

Technological progress also involves an ongoing need for ethical and inclusive development. We must prioritize user autonomy and privacy while maximizing the benefits of technological assistance. This balance is important not only for protecting individual rights but also for ensuring that AI serves the needs of those it aims to support.

By embracing the potential of GenAI while remaining vigilant regarding its ethical implications, researchers, developers, and policy makers can create technologies that not only uplift those who have been historically marginalized but enrich the human experience for us all. In doing so, we may take a step toward a future where technology serves as a platform for inclusivity and empowerment.

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Conflicts of Interest

The author TS is the chief scientist of R&D at Microsoft Israel. The views and opinions expressed here are those of the authors and do not reflect the official policy or position of Microsoft. TS received no financial compensation for his contribution to this work.

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Abbreviations

AI: artificial intelligence
GenAI: generative artificial intelligence

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Adherence to Therapy Using Neurostimulation Devices in the Treatment of Pediatric Attention-Deficit/Hyperactivity Disorder: Extraclinical Study

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Abstract

Background: Pediatric and adolescent patients with attention-deficit/hyperactivity disorder (ADHD) present unique challenges in adherence to device-based therapies outside the clinical environment. The development, approval, and availability of neurostimulation devices for the treatment of ADHD have prompted extraclinical research (ie, outside the sphere of the clinic) on the real-world implementation of such therapies in a population that has difficulty remembering tasks and staying attentive to therapy.

Objective: This study aims to explore the extraclinical pediatric ADHD treatment environment to ensure that design considerations and stakeholder contributions to future innovations are effective.

Methods: Using the Lean LaunchPad methodology with its emphasis on customer discovery and the business model canvas, qualitative analysis methods were applied to elicit the most pertinent themes regarding ADHD treatment in children and the general perception of a new device-based treatment regimen.

Results: Stakeholders expressed a desire that, for innovative ADHD therapies to appeal to children, they include a remote adherence monitoring component and maintain strong evidence of efficacy.

Conclusions: Such barriers to access and desired design features should be strongly considered in the development of neurostimulation therapies for pediatric patients with ADHD. Pediatric and adolescent patients with ADHD require attentive device design considerations to achieve therapeutic adherence in a real-world setting.

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KEYWORDS

pediatric; adolescent; ADHD; neurostimulation; therapy; adherence; real-world; extraclinical; attention-deficit/hyperactivity disorder

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder that manifests in a pattern of inattention and/or hyperactivity-impulsivity that interferes with daily life functions [1-3]. ADHD is classified into three presentations: predominantly inattentive, predominantly hyperactive-impulsive, and a combined type, which is most common [4]. Predominantly inattentive ADHD (formerly known as attention-deficit disorder) is marked by difficulty maintaining focus or paying attention to detail [1]. Predominantly hyperactive-impulsive ADHD (traditionally known as ADHD) is marked by restlessness, fidgeting, and interrupting others [1]. Combined-type ADHD is marked by a combination of the above symptoms that varies by patient but generally involves difficulty with impulsiveness, hyperactivity, and inattention [1]. Identification and understanding of the behavior patterns of children with ADHD are vital to the pursuit of possible treatment options and accommodations [5,6].

The standard of care for pediatric ADHD varies with age and intensity of symptoms but is likely to include a combination of school accommodations, behavioral therapy, and medication

[2,7,8]. For very young patients and/or patients with less-inhibiting symptoms, behavioral therapy is likely to be considered first [9]. Cognitive-behavioral therapy and behavioral parent training programs are proven therapeutic interventions shown to have positive effects in the treatment of ADHD and oppositional defiant disorder (ODD), among other comorbidities [10-13]. In the United States, school accommodations vary by child, school, and schoolteacher, but children with ADHD who meet the necessary criteria are entitled to accommodations through the federally enacted Individuals with Disabilities Education Act (IDEA) and Section 504 of the Rehabilitation Act (Section 504) [14,15]. Such school accommodations include the implementation of management strategies, such as behavioral classroom management and organizational training, and student-specific accommodations, such as extra time on tests, allowing breaks for physical movement, and detailed instructions for assignments [16]. A behavioral classroom management strategy is a well-proven and efficacious intervention that is led by the teacher to encourage positive behaviors and discourage negative behaviors [17,18]. An organizational training intervention strategy teaches the student time management, planning, and organization skills to encourage learning and reduce distractions during schoolwork [17,19]. Despite the well-studied benefits that these interventions can provide to children with ADHD, there is significant difficulty in the real-world implementation of such interventions, and the accessibility of school services varies widely across various sociodemographic groups [20-22]. Stimulant medications are the primary form of pharmacotherapy for children with ADHD, despite the considerable side effects experienced by most patients [9,23]. The most researched stimulant medications are the dopamine and norepinephrine transporter blocker, methylphenidate, which serves as the first-line pharmaceutical intervention, and amphetamines, central nervous system stimulants that serve to focus attention and improve executive function through increased release of norepinephrine and dopamine in the prefrontal cortex [24]. Methylphenidate, while a first-line pharmacotherapy for clinical ADHD, is subject to abysmal adherence [25], which has prompted growing interest in single-dose therapy [26]. Most stimulant medications exhibit a pharmacodynamic profile of a quick onset of therapeutic effects and short duration of action (varying from approximately 2 - 12 h) and therefore must be taken any time focused attention and/or improved executive functioning is desired [27,28]. While school accommodations, behavioral therapy, and medication are the most studied interventions for pediatric patients with ADHD, there are still significant shortcomings in these interventions regarding accessibility, cost, and efficacy. These shortcomings can be addressed by the development of technology-based solutions, such as neurostimulation [29,30].

Recent developments in the neurological and psychological etiology of ADHD have led to increased innovations, resulting in new therapeutic interventions [2,31]. Neurostimulation is one such innovation that has begun to be developed as an alternative or adjunctive treatment for ADHD in children [31-33]. Neurostimulation, or the purposeful modulation of the nervous system's activity, seeks to modulate brain activity and improve attention, impulse control, and executive function in children with ADHD [32]. These devices use different strategies, being invasive (eg, deep brain stimulating microelectrodes) or noninvasive (eg, transcranial stimulation including repetitive transcranial magnetic stimulation [TMS], transcranial direct current stimulation [tDCS], or external trigeminal nerve stimulation [TNS] methods. TMS noninvasively uses magnetic fields to induce electrical currents in specific regions of the brain). Typically, TMS targets the dorsolateral prefrontal cortex (DLPFC) or other relevant networks associated with ADHD symptoms. TMS has been explored for both short-term symptom management and long-term modulation of brain networks. tDCS uses low-intensity electrical currents to modulate neuronal excitability. Typically, tDCS targets the DLPFC, which is implicated in attention and impulse control. Studies show potential improvements in attention and executive function. TNS delivers mild electrical stimulation to the trigeminal nerve via electrodes placed on the forehead. TNS, Food and Drug Administration (FDA)–approved for pediatric ADHD treatment, is believed to influence arousal- and attention-regulating brain structures, such as the locus coeruleus and prefrontal cortex.

For the treatment of ADHD, tDCS and external TNS represent, even against the backdrop of small clinical studies, promising interventions [34]. tDCS has been shown to reduce clinical manifestations of ADHD and may be able to improve memory and attention performance, but remains in pilot studies and has not been approved by the FDA [33]. External TNS can be achieved noninvasively, with external electrodes and an on-body pulse generator, or invasively, with subcutaneously implanted electrodes and an implantable pulse generator [33]. External TNS transmits small electrical currents transcutaneously via supraorbital electrodes adhesively attached to the skin over the supratrochlear and supraorbital branches of the ophthalmic nerve [2]. The supraorbital branch has many connections to the brain and, when stimulated, may influence the bioavailability of electroceuticals, such as catecholamines, that potentiate ADHD symptoms [35,36]. NeuroSigma was the first company to receive FDA clearance for a neurostimulation device with a pediatric ADHD indication, called the Monarch eTNS System [37]. The Monarch device consists of a main component that generates pulses to stimulate the trigeminal nerve and an electrode array accessory to deliver the pulses [38]. It operates using radio frequency energy for over 8 hours, but the duration of treatment for each patient is determined by the physician. At present, there is no clinical evidence to support a specific timeline, frequency, or length of treatment when using Monarch. The device can deliver between 0.2 and 10.0 mA at a frequency of 120 Hz. The Monarch is battery-operated, rechargeable, and involves minimal steps to assemble and use. The kit is sold for around US $1000, with enough disposable electrode pads for 4 weeks, and additional electrode pads are sold for US $70. Neurostimulation offers pediatric patients with ADHD a promising, powerful treatment option, which is sure to gain traction as the technology develops further.

tDCS of the left and right DLPFC, using an anodal protocol, is most often used [39,40]. Safety and patent-specific or personalized stimulation parameters have not been systematically examined [41]. Using currents of 1 - 2 mA applied directly to the scalp via contacting electrodes, tDCS appears effective in addressing clinical symptoms and

neuropsychological deficits of patients with ADHD with no observable serious adverse effects [41]. There remains, however, considerable opportunity to address device engineering parameters such as field strength, polarity, and/or duty cycle and duration in relation to larger, appropriately diverse clinical trial cohort sizes.

The emergence of noninvasive neurostimulation technologies for the treatment of ADHD [30,33,42] heralds a new era in therapeutic options for large populations of pediatric patients [32,43]. However, stakeholders in the extraclinical (outside the sphere of the clinic) use of neurostimulators among children—parents, teachers, school nurses, and psychologists—are rarely consulted and have little opportunity for preclinical or extraclinical input into design considerations that support adherence to therapy using such devices [8,31]. As new devices and neurostimulation options are made available in the ADHD care environment, careful attention must be paid to stakeholders' preferences, desires, and obstacles to treatment. This paper evaluates stakeholder input into design considerations in the development of neurostimulation technologies for the treatment of ADHD. While based on a small number of participants, the findings nonetheless suggest the need for further proactive engagement with the broader stakeholder community in guiding the development and clinical application of noninvasive neurostimulation for the treatment of ADHD.

Methods

Overview

The Lean LaunchPad is an evidence-based, experiential program created by Blank [44] that guides the testing and validation of product-focused ideas using real customer feedback. Combining principles from customer development and business model generation, the Lean LaunchPad reduces the risk of building products no one wants by focusing on validation through real-world customer interactions, pivots, and evidence-based decisions rather than assumptions. It is widely used in startup accelerators, universities, and corporate innovation programs as a practical framework for launching new product-based ventures. Customer discovery allows biodevice development teams to engage directly with potential customers to validate or invalidate their clinical use assumptions and to understand the needs, problems, and potential solutions from the customers' perspective. The business model canvas maps key components of the business model, including value propositions, customer segments, channels, revenue streams, and more. This canvas serves as a dynamic tool that evolves based on feedback and findings from customer discovery interactions. The Lean LaunchPad is widely used by biomedical engineers in academic settings, accelerators, and incubators to help developers gain a deep understanding of their market, build products that meet real customer needs, and increase their chances of clinical success.

Identification of Stakeholders

Identified stakeholders in the pediatric ADHD treatment environment included parents of children with ADHD, patients with ADHD, schoolteachers, school nurses, pediatric health care providers, and psychiatric health care providers. These stakeholders form a complex web of interested parties influencing adherence of children with ADHD to their prescribed treatment regimen. Interviewees were selected by drawing a 50-mile radius from the College of Medicine at Texas A&M University (Bryan–College Station area), which was subsequently extended to the whole state of Texas. Clinics and clinicians were identified from the membership of the Texas Psychological Association and the subset identified with practices that served children with ADHD. Schoolteachers, school nurses, parents, and patients were identified within the Central Texas community by the authors. At the end of each interview, interviewees were asked for referrals to another stakeholder who might offer a unique perspective, if the interviewer felt it appropriate. This served to establish a network of stakeholders with diverse backgrounds and opinions. The final stakeholder community consisted of 1 parent of 4 children with ADHD, 6 patients with ADHD, 2 schoolteachers, 4 school nurses, 8 pediatric health care providers, 4 psychiatric health care providers, and 5 additional general health care providers, for a total of 30 individuals.

Interview Methodology

A series of questions guided by the Lean LaunchPad methodology was formulated for the semistructured interviews, with three groups of questions exploring the problem, solutions, pricing, and possible "go-to-market" strategies (Multimedia Appendix 1). The same questionnaire was used for all interviewed stakeholders to enable more rigorous analysis. Thirty stakeholders were contacted and scheduled for a ~15-minute interview via video or phone, in compliance with Texas A&M University, local, and national COVID-19 social distancing guidelines. The list of questions was sent to interviewees in advance via email. Most interviews were recorded for transcription, with interviewee consent. If consent was not granted by the interviewee for recording (2 of 30 interviewees), the interviewer took detailed notes of the conversation and question responses. This work includes answers from thirty total individuals: 4 psychiatric health care providers, 8 pediatric health care providers, 5 other health care providers, 4 school nurses, 2 schoolteachers, 6 patients, and 1 parent of 4 patients, as shown in Table 1.

Responses were transcribed and recorded in a Microsoft Excel spreadsheet by the interviewer after conclusion of the interview.

Table . Composition of the interviewed stakeholder group.

Stakeholder	Value, n (%)
Patients	6 (20.0)
Parent	1 (3.3)
Psychiatric HCP[a]	4 (13.3)
Pediatric HCP	8 (26.7)
School nurse	4 (13.3)
Schoolteacher	2 (6.7)
Other HCP	5 (16.7)

[a]HCP: health care professional.

Data Analysis

Transcribed answers were subject to thematic analysis for each question. Thematic analysis is a well-established qualitative research methodology in which interview transcripts are carefully read to extract key ideas and meanings, providing a deeper understanding of the phenomenon under study. This process allowed us to identify, analyze, and interpret recurring patterns or "themes" within the dataset. The thematic analysis was conducted in three main stages: data processing, theme development, and final analysis. Data processing included transcription and initial coding. Stakeholder interviews were recorded and transcribed by the interviewer, with the responses roughly sorted by question set and question number. The first pass of analysis involved highlighting sections of text, whether words or phrases, and using a few words to describe the highlighted content, referred to here as "codes." The full transcript of every interview was reviewed, and codes were created for any interesting, relevant, or unique information identified in the transcripts. These coded text sections were then rearranged and sorted, such that all text supporting a specific code could be viewed together. The codes created during the initial data processing stage are listed in Textbox 1.

Upon review, irrelevant and/or infrequent codes were removed from the list, and others were combined or separated as needed. Similar codes were loosely grouped together into themes, which were preliminarily named. Transcripts were then reanalyzed according to the themes, verifying that the themes did not over- or under-represent certain ideas in the data. Codes and themes were edited and adjusted as needed. The finalized themes are listed in Textbox 2.

A short definition for each theme was written to further describe how the theme was manifested in the transcripts and how it related to the larger analysis of the stakeholder investigation process.

Textbox 1. Initial codes created during data processing.

Problem

- Controlled substance
- Misuse concerns
- Cost
- Social stigma
- Forgetfulness
- Parental involvement
- Comorbidities
- Difficulty swallowing pills
- Difficulty finding a suitable medication
- Side effects from medication
- Contraindications to medication
- Multi–attention-deficit hyperactivity disorder–child families

Solution

- Appeal to children
- Health care professional supervision
- Parental supervision
- Evidence of effectiveness
- Brand-name medication
- Generic medication
- Behavioral therapy
- Neurofeedback therapy
- Hyperbaric therapy

Pricing and go-to-market

- Primary care clinic pays
- Specialty clinic pays
- Patient pays
- Price

Textbox 2. Finalized themes created during analysis.

Problems

Barriers to access

- Controlled substance and overall fear of misuse
- Costs
- Social stigma

Barriers to adherence

- Inherent attention-deficit/hyperactivity disorder traits
- Parental involvement
- Comorbidities
- Difficulty swallowing pills

Barriers to prescription

- "Trial and error" strategy
- Medication side effects

Solution

Desirable features

- Appeal to children
- Remote adherence monitoring (health care professional and parent)
- Evidence of effectiveness

Available and known treatment modalities

- Brand-name medication
- Generic medication
- Behavioral therapy
- Neurofeedback therapy
- Hyperbaric therapy

Pricing and go-to-market

Purchasing models

- Primary care model
- Specialty clinic model
- Patient purchase model

Ethical Considerations

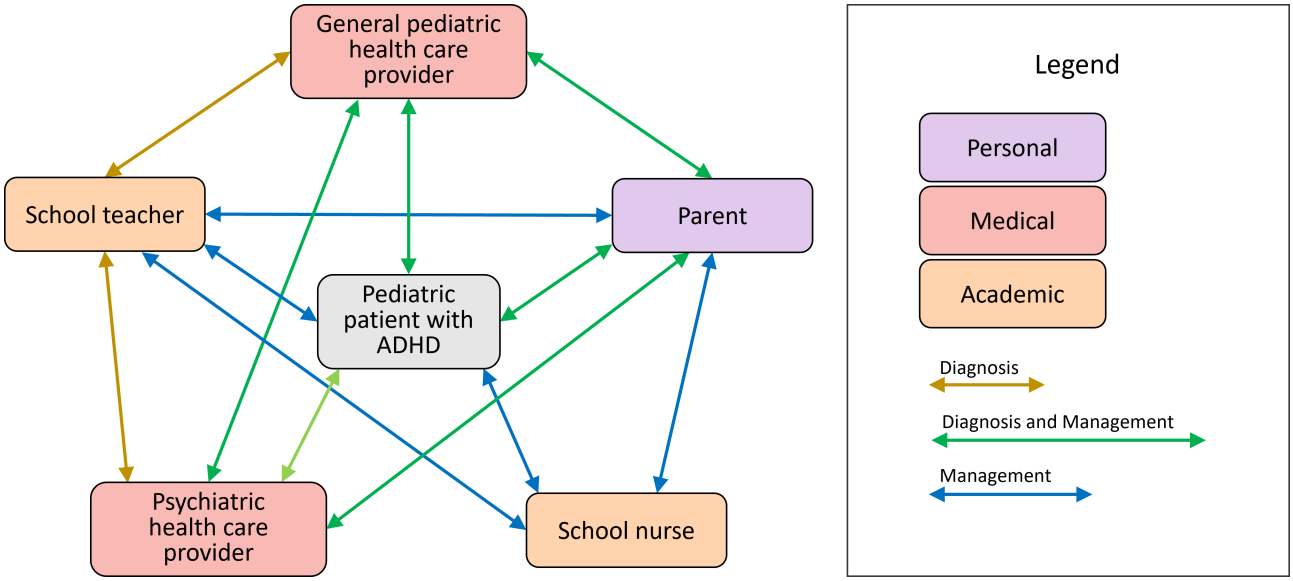
All participants in this study provided individual informed consent to be interviewed. All participants were deidentified and no compensation was provided for their participation. Ethical approval for this study was granted by the Texas A&M University Institutional Review Board under study number IRB2020-0898D (institutional review board title: Enhancing Therapeutic Device Adherence of Children with ADHD: An Efficacy Trial).

Results

Stakeholder Environment and Relationships

The information gained from these interviews revealed a complex web of interactions between general pediatric health care providers, psychiatric health care providers, schoolteachers, school nurses, parents of patients, and pediatric patients, as shown in Figure 1.

Figure 1. Pediatric attention-deficit/hyperactivity disorder treatment stakeholder environment, involvements, and their interactions. ADHD: attention-deficit/hyperactivity disorder.



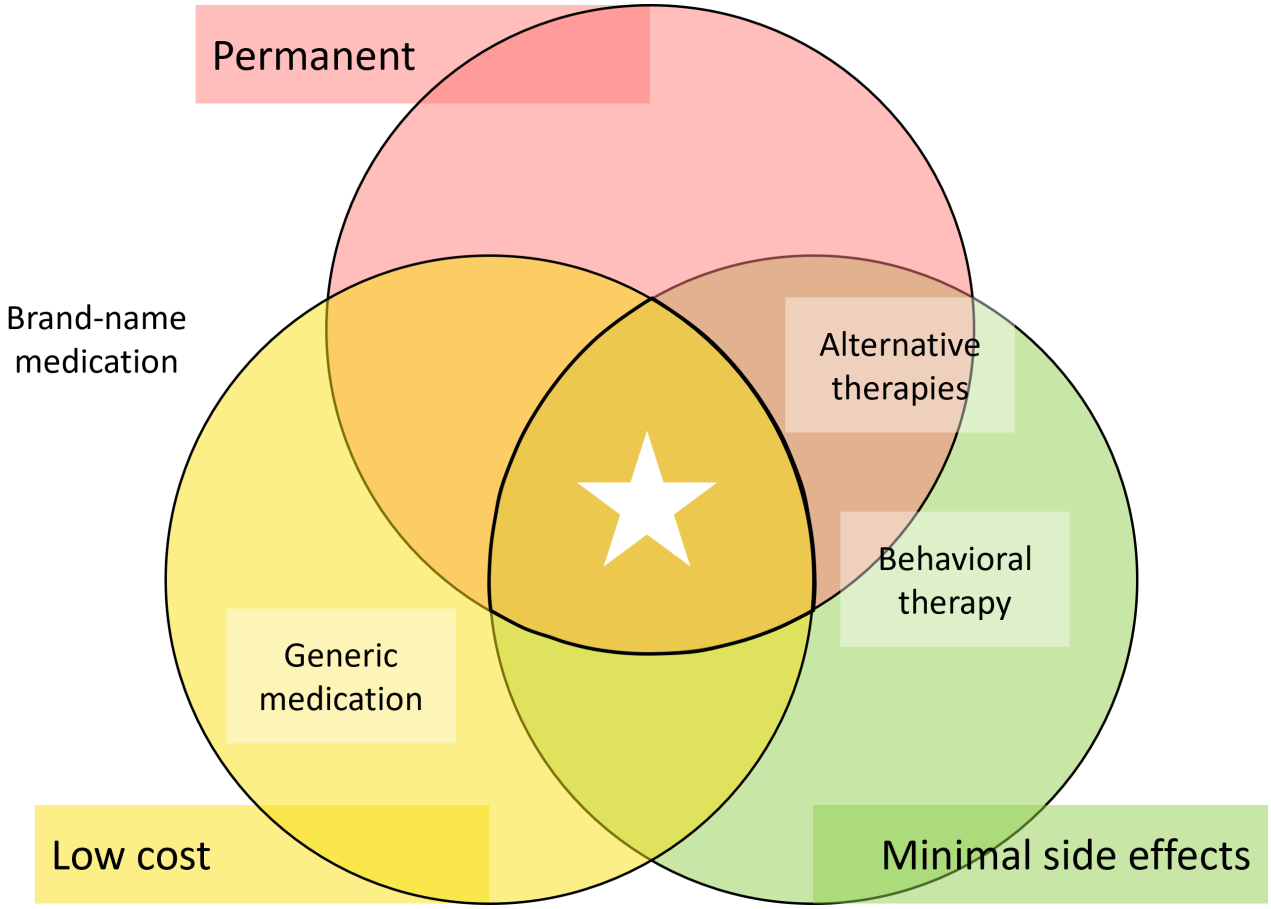
Barriers to Treatment Access

This work identified three key barriers to the access of ADHD treatment options: fear of misuse, cost, and social stigma. In addition, the work identified four key barriers to adherence to stimulant treatment: (1) inherent ADHD traits, (2) parental involvement, (3) comorbidities such as ODD [45], and (4) difficulty swallowing pills, dysphagia [46,47].

Desired Clinical Features of Treatment Modalities

Through the stakeholder investigation process, three desirable extraclinical features of a "perfect" ADHD treatment solution were identified (1) low cost, (2) permanence, and (3) minimal side effects. The Venn diagram of Figure 2 schematically illustrates the balance of these features among the various treatment options.

Figure 2. Desirable clinical features of attention-deficit/hyperactivity disorder treatment in relation to current treatment options.



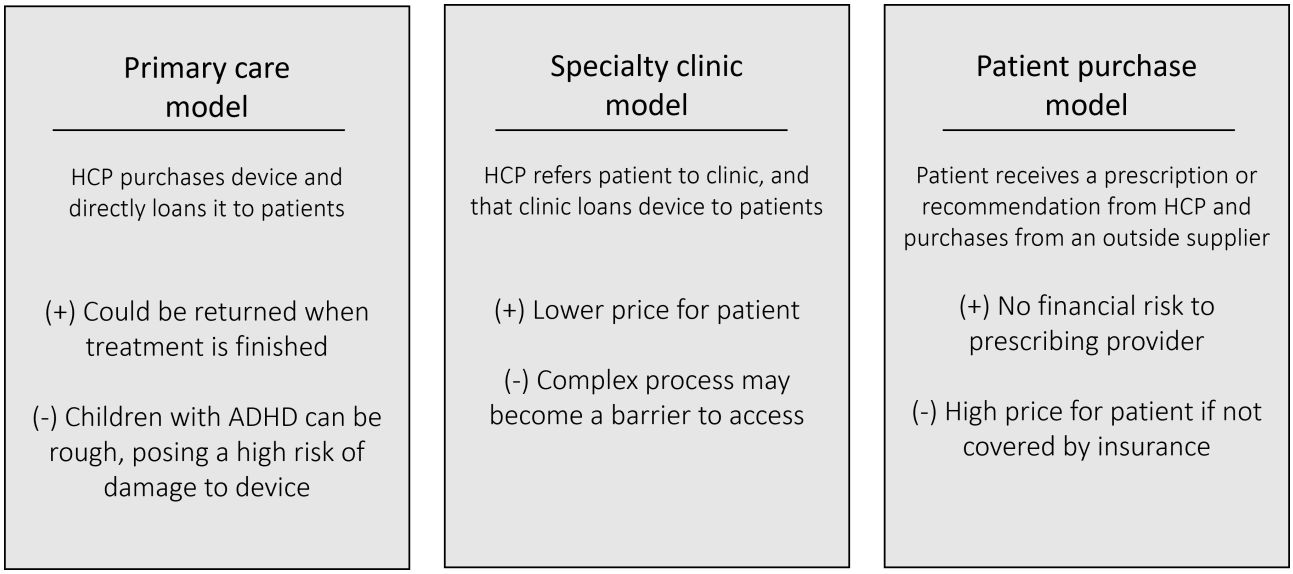
Desired Usability Features of Treatment Modalities

Two desirable usability features for future treatment modalities were elucidated after a minimal introduction to neurostimulation devices, which are as follows: (1) appeal to children and (2) adherence monitoring.

Device-Based Treatment Purchase Options

Of the 3 therapeutic access models presented to stakeholders, shown in Figure 3, the patient purchase model was the most popular among the interviewed stakeholders.

Figure 3. Purchase option models proposed and presented to stakeholders. ADHD: attention-deficit/hyperactivity disorder; HCP: health care professional.



Identified Advantageous Entry Markets

Three highly specific entry markets were identified: (1) multi-ADHD-child families, (2) families desiring conservative treatment modalities, (3) patients requiring brand-name medication, and (4) patients with contraindications to stimulants.

Discussion

Stakeholder Environment and Relationships

Each party (Figure 1) plays a specific role in the diagnosis and management of pediatric ADHD, often interacting with one another and influencing each other's actions. Generally speaking, a diagnosis is made upon self-reporting to either a general pediatric health care provider or a psychiatric health care provider by the patient, their parents, and/or their schoolteacher. Once a diagnosis is made, the patient is clinically managed by their parents, health care providers, and sometimes, the school nurse. Some patients are diagnosed and managed exclusively by a general pediatric health care provider, some exclusively by a psychiatric health care provider, and some are diagnosed and managed concomitantly by a general pediatric health care provider and a psychiatric health care provider. This largely depends on the comfort level of the general pediatric health care provider with pediatric psychiatry and the presence of possible comorbidities that may complicate the process and be better handled by a psychiatric professional. Health care providers involved with a specific patient are responsible for clinical management and the administration of pharmacotherapy. The schoolteacher is responsible for managing the patient's behavior in the classroom, while the school nurse oversees behavioral management in the broader school environment outside the classroom. If the patient is on immediate-release stimulant pharmacotherapy, the schoolteacher is generally the first to notice a missed dose on a specific day, as their behavior will be affected when the child arrives at school. This is where the school nurse's responsibilities become apparent, including administering medication for patients requiring mid-day dosing and managing side effects that occur during school hours. Finally, the parents of a pediatric patient with ADHD are largely responsible for all the activities surrounding treatment, as they advocate for and represent their child throughout the process. All these parties must be in regular communication with one another to ensure optimal diagnosis and clinical management of a pediatric patient with ADHD.

Barriers to Treatment Access

The three key barriers to access to ADHD treatment options—fear of misuse, cost, and social stigma—have pragmatic origins. Health care providers and parents alike are often concerned about possible misuse of stimulant medication, given that most are schedule II controlled substances [48]. Because of this classification, health care providers, under normal circumstances, cannot prescribe more than 30 days' medication at a time and must follow up with each patient approximately once per month [49]. This research perceived a significant fear of misuse among prescribing physicians and parents alike. Another identified barrier to access to stimulant medications is cost. Depending on which type of medication is prescribed and is found to work well for the patient, the cost of monthly medication can, in many cases, be prohibitive. This can be ameliorated by seeking insurance coverage for a specific stimulant medication or circumvented altogether by finding an alternative medication option that is already covered by the patient's insurance. One general pediatric health care provider stated that "it is hard to find a prescription and medication that is effective and helpful for the patient, while also being covered by insurance." An additional barrier to access to stimulant

medications is the perceived social stigma surrounding their use. This theme was most prominent among interviews with general pediatric health care providers, as several mentioned situations in which they felt a patient was a great candidate for stimulant medication, but the parents of the patient were extraordinarily hesitant to start their child on stimulants. One physician elaborated on the familial strife this can cause, noting that when parents hesitate to start their child on stimulants, it "creates frustration and difficulties for the patients themselves." Only one physician was able to pinpoint what exactly she felt was causing the social stigma, stating that it was "from fear that the stimulants could cause addiction problems later." There is substantial evidence in the literature showing no such association between stimulant use and substance use disorder in patients with ADHD, even when stimulant treatment is initiated in childhood [50-55]. More research must be done and more effective communication engendered to further clarify the absence of association between stimulant medication and substance use disorder comorbidity in ADHD.

Four key barriers to adherence to stimulant treatment were identified during the stakeholder investigation process, including inherent ADHD traits, parental involvement, comorbidities such as ODD [45], and difficulty swallowing pills, dysphagia [46,47]. Patients with ADHD are, by definition, inattentive, hyperactive, and impulsive, and thus do not have favorable traits for adhering well to strict medication schedules. A patient's adherence to stimulant medication varies from patient to patient and is found to be highly dependent on the level of parental involvement that the patient experiences. The importance of parental involvement was mentioned 16 times throughout the interviews, most stating that "compliance [to medication] without parents is extremely low…with parents, the number [adherence rate] is higher." A noteworthy point is that, because of ADHD's highly heritable nature, the possibility of a parent of a patient having ADHD is higher than average [56,57]. Therefore, adherence to medication can be affected not only by the child's condition, but also by that of the engaged parent. Comorbidities to ADHD were also frequently mentioned in the interviews, including obsessive-compulsive disorder, autism spectrum disorder, ODD, and bipolar disorder. These findings are consistent with the literature on common comorbidities with ADHD [58]. Specifically, ODD can create difficulty with adherence to treatment, as patients with ODD are inherently defiant of authority and argumentative [1].

There are also barriers to finding an effective and tolerable medication type and dosage. Patients and physicians expressed that identifying the most effective medication and dosage for the patient's specific ADHD symptoms was extremely difficult. The most common strategy was simply "trial and error" with medications, in some cases taking several years before a suitable medication and dosage were found. The therapeutic window for most stimulants is narrow, with the optimal dosage often laborious to find for each patient, and the increase in side effect severity occurring rapidly outside the therapeutic window. Stimulant side effects were the most frequently mentioned topic in this study, with 43 mentions overall. The side effects of stimulant medication can be harsh and can significantly complicate ADHD management, particularly in children. One adolescent patient stated:

> *The side effects can really impact your life. I've been taking medication for years, since elementary [school]. I know in elementary [school], some people would ask me if I was mad at them because I was not as creative or expressive as before. The medicine sometimes doesn't make you feel like yourself.*

This theme, of stimulant medication causing a patient to not "feel like themselves," was echoed by many of the young adults with ADHD interviewed. They were quite sincere in their discussion about the side effects they experienced and discussed how impactful this feeling had been in their social and familial relationships.

Desired Clinical Features of Treatment Modalities

The three desirable clinical features of a "perfect" ADHD treatment solution—low cost, permanence, and minimal side effects—are partially met by the most common existing treatment options: pharmacotherapy [7], behavioral therapy [59], and complementary and alternative therapies [60]. Each of the common treatment options addresses some of these desirable features, but none addresses all three, as shown in the Venn diagram of Figure 2. A distinction is drawn between generic and brand-name medication options due to the drastic difference in cost to the patient.

Brand-name medication is neither permanent nor low-cost and has significant side effects. Generic medication may be low-cost, but it is also not permanent and may have significant side effects. Behavioral therapies have minimal side effects and can be permanent but are generally not and can be quite costly for patients. Alternative therapies can claim to be more permanent with less side effects but are very high cost, and generally the effectiveness is not well-proven in the literature [61]. Alternative therapies included in this work are hyperbaric oxygen therapy and neurofeedback therapy. Despite its lack of the key desirable features identified above, stimulant medication is the most prominent and popular treatment option discussed in these stakeholder interviews. Neurostimulation devices could meet these desired clinical features, as the modality is developed to be permanent with minimal side effects, and over time, could be offered at a low cost over the lifetime of the device and the duration of therapy [2].

Desired Usability Features of Treatment Modalities

Neurostimulation therapy, notably tDCS, for example, requires wearing a headset for 20 minutes each day for 10 consecutive days, which was disclosed to participants. Two desirable usability features for future treatment modalities were elucidated after this minimal introduction to neurostimulation devices: (1) appeal to children and (2) adherence monitoring. Many stakeholders discussed the need for treatment to be appealing to children in some way to engage them in the treatment process and consequently, ensure ownership of the therapy. One schoolteacher stated the following insight on the importance of appeal to children:

> *It depends on how it is presented. Some kids do not even like glasses, [because] they want it to be seen*

> *as "cool." They [children with ADHD] would probably be more apt if they could wear it [a novel treatment device] with a hat. Kids are likely willing to try.*

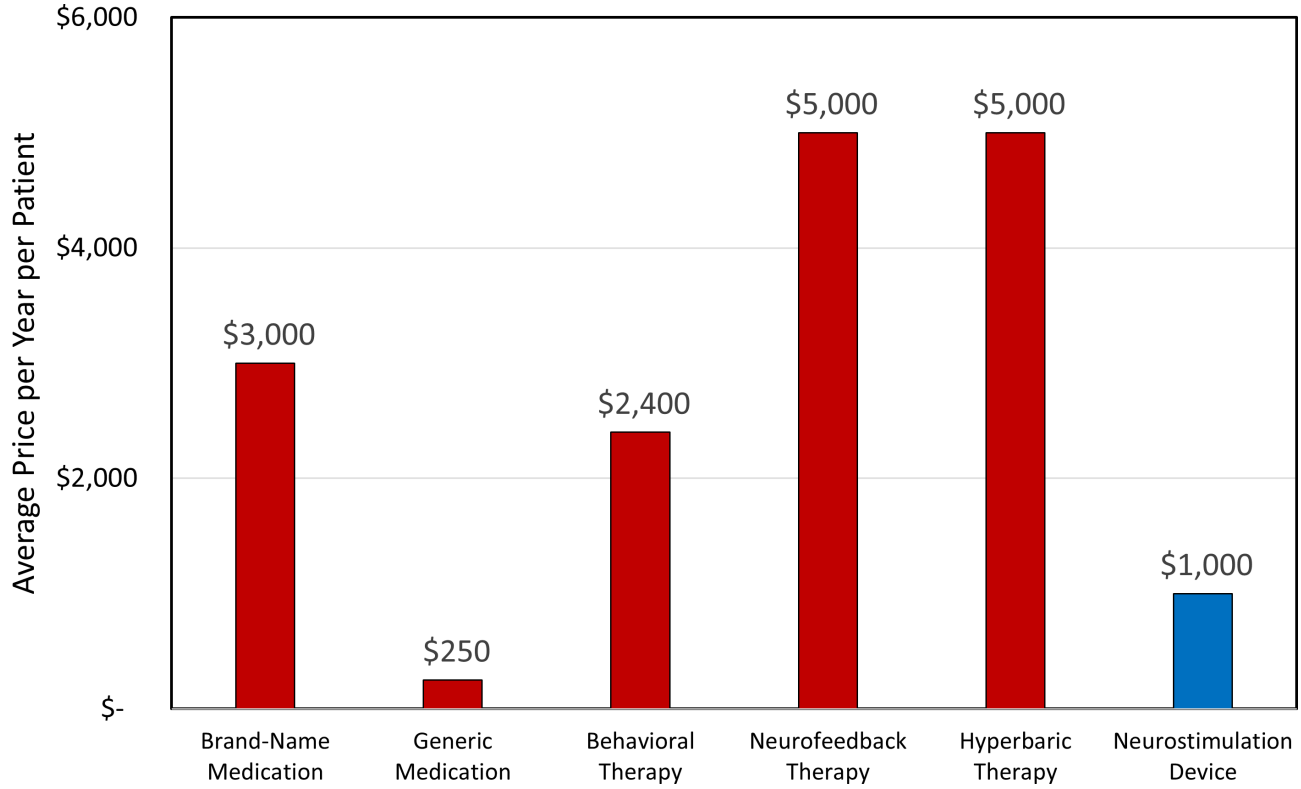
Two of the psychiatric health care providers echoed this sentiment, stating the vital need for emotional, creative, or imaginative appeal for children with ADHD to engage with the device. These observations point to the need for design features of color, texture, and form factor that promote, rather than dissuade, engagement with the therapeutic device [8]. An important consideration was that electrodes contacting the scalp should be designed to make contact through hair of various types and textures. This suggests the use of brush-type electrodes with bristles of conductivity to deliver the stimulating current and sufficient elastic modulus sufficient to penetrate hair of multiple textures to contact the scalp [62-64]. Suitable electrical conductivity is typically achieved using an electrolyte-filled sponge to first bathe the electrodes. New electrode materials that permanently retain electrolyte can render the system "plug-and-play," without the need for preparing the electrodes with saline-soaked sponges. An additional feature requested by general pediatric health care providers and patients was that of remote adherence monitoring. Physicians reported appreciating the compliance estimate made available by looking at pharmacy refill requests and expressed interest in seeing data on patient usage for a treatment device in the home. Patients also stated that they would prefer for their clinician to "closely monitor [their] treatment and usage of the device." Both an appeal to children and an adherence monitoring system should be closely considered in the usability development of upcoming pediatric ADHD treatment modalities [8].

Device-Based Treatment Purchase Options

The primary care model shows that a primary care provider or general practice clinic purchases the device and then supplies it to its patients for the duration of the prescription. The largest advantages to this loaner model are that the device could be returned when treatment was finished, likely reducing the overall cost of treatment for the patients, and the device could be sanitized and reissued for use. The largest drawback to this model is that children with ADHD are generally hyperactive and impulsive, thus increasing the risk of damage to the device while it is loaned out to the patient. This incurs difficulty on the part of the primary care physician, as the devices may quickly become damaged and/or unusable. The specialty clinic model shows that when a primary care provider identifies a patient as a good candidate for neurostimulation treatment, they refer that patient to an outside clinic, which manages the treatment course and loans devices out to patients. The most significant benefit of this model is that it could reduce the price of treatment to patients and remove some of the responsibility of implementing new technology from the primary care provider. The most significant disadvantage to this model is that the added step in the process may unnecessarily complicate the system and may become a barrier to access for patients. The patient purchase model shows that a patient receives a prescription for neurostimulation treatment from their health care provider and then purchases the device themselves from an outside supplier. The most compelling advantage to this model is that it requires no financial risk on the part of the prescribing provider, increasing the likelihood of the device being prescribed overall. The most compelling disadvantage to this model is the high cost, which is the full responsibility of the patient. Despite this point, the patient purchase model was the most popular among interviewed stakeholders because of the ease of accessibility to treatment and the low financial risk required from providers.

Interviewees reported their perception of the average price of various ADHD treatments with which they were familiar. These estimates were analyzed and distilled into five categories: brand-name medication, generic medication, behavioral therapy, neurofeedback, and hyperbaric therapy, as shown in maroon in Figure 4. The interviewees were also asked to report approximately what price they thought was appropriate for one round of neurostimulation treatment for ADHD, which is shown in blue in Figure 4.

Figure 4. Reported average price (in US dollars) per year of selected attention-deficit/hyperactivity disorder treatment modalities and projected price (in US dollars) per intervention using neurostimulation device therapy.



Identified Advantageous Entry Markets

Throughout the analysis of the stakeholder interviews, a few key advantageous entry markets were revealed. These highly specific entry markets have unique pain points that are neglected by current pediatric ADHD treatment modalities. These markets include multi-ADHD-child families, families desiring conservative treatment modalities, patients requiring brand-name medication, and patients with contraindications to stimulants. Multi-ADHD-child families are somewhat common due to the high heritability of ADHD. Over time, neurostimulation could prove to be a highly cost-effective option for families requiring pharmacotherapy for several children over many years. Many stakeholders expressed concern about the large population of families who feel a social stigma surrounding stimulant medication and generally desire more conservative treatment for their children. A neurostimulation device could offer them effective treatment without the use of stimulant medication. Patients who require brand-name medication would also be a key entry market, as brand-name stimulant medications carry extremely high costs for patients. The final key entry market identified in this study is patients for whom stimulant medication is contraindicated, including those with symptomatic cardiovascular disease, hyperthyroidism, hypertension, and/or a history of substance use disorder, among other things [65,66]. For these patients, there are currently very few options of any kind for long-term, effective management of ADHD. The population with pharmacological contraindications is a primary entry market for neurostimulation devices for the treatment of pediatric ADHD.

Limitations of the Study

This study draws upon a relatively small number of stakeholders, but an otherwise broad set of representative stakeholders in ADHD therapy. Extrapolating from this small data set is one limitation. Second, the stakeholders are from a region, initially within a 50-mile radius of the College of Medicine at Texas A&M University and eventually expanding to the entire State of Texas. There may be a regional predisposition toward technology interventions among practitioners who work near a research-intensive, engineering-centric university. The underwhelming participation by parents, an important stakeholder group in ADHD therapy, is noteworthy. Finally, participants were purposively selected rather than randomly sampled.

Future Work

The stakeholder engagement results could be strengthened with the addition of more interviews, particularly those with parents and/or guardians of children with ADHD, as the children themselves are not particularly available for or willing to complete such interviews. In addition, another round of interviews could be conducted with more precise questions to elucidate more exact pain points, desired solutions, and purchase options. Both supplementary propositions would require additional time, effort, and funding that were out of the scope of this body of work.

Conclusions

A customer discovery process, as outlined by the National Science Foundation Innovation-Corps, was designed and executed to investigate the pediatric ADHD treatment environment. Thirty stakeholders were interviewed using

semistructured interview methodology, and their responses were recorded and analyzed for key themes and insights. A specific interest was placed on the developing technology of neurostimulation for the treatment of pediatric ADHD, and the stakeholders gave insightful feedback on problems in the pediatric ADHD treatment environment, important desired features to be considered in the development of a new treatment modality, and purchase option modeling for the distribution of neurostimulation devices throughout the market. These sessions revealed a complex web of stakeholders involved in the diagnostic and therapeutic management of a child with ADHD. Numerous key barriers to treatment access were identified, clarifying the difficulty that stakeholders face when choosing a treatment regimen. A major "pain-point" for pediatric patients with ADHD in their current treatment options was identified in the side effects, high cost, and impermanence, which could be mitigated with the development of therapeutic neurostimulation devices. Stakeholders desired a new treatment modality that had specific usability features of (1) a creative or social appeal to children, and (2) an adherence monitoring system. Investigation regarding the stakeholder-desired purchase method of a device-based treatment modality revealed that a patient purchase model was the most popular because of the ease of accessibility to treatment and the low financial risk required from prescribing providers. Several advantageous entry markets were identified for a device-based pediatric ADHD treatment option, including multi-ADHD-child families, families desiring conservative treatment modalities, patients requiring brand-name medication, and patients with contraindications to stimulants. Overall, this work revealed a niche need for the development of a new ADHD treatment modality, and neurostimulation appears to be a hopeful option in this regard.

Acknowledgments

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Data Availability

The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AC, SB, and AGE contributed to the concept and outline of the manuscript. AC and AGE prepared the early draft, with AC and AGE also responsible for detailed writing, reviewing, and editing. SB and AGE provided essential resources.

Conflicts of Interest

AGE is the founder, president, and scientific director of ABTECH Scientific, Inc, a manufacturer of microfabricated electrodes and devices used in biomedical diagnostics and the measurement of physiological data. SB is cofounder and chief technology officer at Corinnova; cofounder and chief operations officer at Shape Memory Medical; cofounder of Pulmonescence Diagnostics; and founder, chairman, and chief executive officer at Velostim. The funding sponsors had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript; and in the decision to publish the findings.

Multimedia Appendix 1
Stakeholder interview questions.
[DOCX File, 48 KB - neuro_v4i1e68736_app1.docx]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
DLPFC: dorsolateral prefrontal cortex
FDA: Food and Drug Administration
IDEA: Individuals with Disabilities Education Act
ODD: oppositional defiant disorder
tDCS: transcranial direct current stimulation
TMS: transcranial magnetic stimulation
TNS: trigeminal nerve stimulation

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A Game-Based Mechatronic Device for Digital Rehabilitation of Hand Function After a Stroke: Design, Prototyping, and Feasibility Study

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Abstract

Background: This paper presents an easy-to-use, affordable robotic manipulandum device (RMD) equipped with smart monitoring and assistive technologies to engage in game-based exercise and repetitive task practice. The RMD has been designed to enhance a wide range of fine motor manual dexterity skills, including thumb, finger, and wrist movements. By focusing on finger and hand functions, it extends its utility beyond basic reaching or object transfer movements. Various interchangeable 3D-printed therapy handles of different shapes and sizes can be easily attached to the RMD drive shaft. These handle movements can be used to engage with numerous affordable, commercially available computer games, allowing patients to practice tasks that involve varying movement amplitudes, speeds, precision, and cognitive challenges. Additionally, the device is capable of automatically recording and storing the patient's real-time performance data on any given computer, integrating assessment into treatment.

Objective: A pilot study was conducted with 5 patients with stroke to examine the feasibility and benefits of a 6-week game-based exercise program using the proposed device.

Methods: A feasibility study was conducted with 5 participants. Data were collected using the computer game–based upper extremity assessment of manual dexterity and Wolf Motor Function Test (WMFT) before and after the intervention lasting 6 weeks.

Results: The pilot study demonstrated that clients' expectations related to manual dexterity were met. The average improvement in the functional ability score of the WMFT was 14 (SD 3) points, with all participants exceeding the minimal clinically important difference. The average reduction in total time was 30 (SD 14) seconds, with 4 of 5 participants surpassing the minimal clinically important difference. For the computer game–based upper extremity assessment, the average improvement in success rate was 23% (SD 12%), and the average decrease in response time was 105 (SD 44) milliseconds.

Conclusions: Findings revealed acceptable, engaging, game-based, and task-oriented training with a high level of compliance. Substantial improvements from pre- to postintervention were observed using the WMFT and assessments of manual dexterity.

Trial Registration: ClinicalTrials.gov NCT05071885; https://clinicaltrials.gov/study/NCT05071885

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KEYWORDS

stroke; manual dexterity; hand function; poststroke; fine motor; thumb; finger; wrist; movement; motor rehabilitation; assistive technology; smart monitoring; pilot; feasibility; prototyping; prototype; nervous system; nerve; motor neuron

Introduction

Background

Upper extremity (UE) motor impairments and persistent hemiparesis commonly lead to difficulties with manual dexterity after a stroke [1]. Manual dexterity, defined as the ability to manipulate objects, is crucial for many everyday tasks, both for leisure and social interactions. These tasks often require the manipulation of objects that vary widely in physical properties and functional demands, necessitating a high degree of precision [2]. Individuals with chronic sensory-motor deficits in the UE following a stroke can greatly benefit from intensive, well-resourced therapy services [3-6]. A novel approach to enhance patient engagement in therapy is the use of computer

games, which integrate various learning elements and present motor and cognitive challenges. This allows individuals to participate in focused, task-specific activities with a significant number of repetitions [7-10]. Several gaming systems have been used as rehabilitation tools [11]. Various computer input devices have been used to detect arm segments or finger motions. The corresponding motion signals are used to interact with digital avatars or objects [12,13]. However, these game-based exercise programs often fail to adequately address object handling and fine motor function–based object manipulation. Consequently, they do not account for the sensory, tactile, or proprioceptive signals from the hand that are essential for effective goal-directed object manipulation tasks. To enhance the brain's capacity for learning, it is vital to create experiences that improve manual dexterity through guided and repetitive practice of manipulation tasks requiring precision [14-16]. Some game-based rehabilitation systems use handles or joysticks as controllers [17,18], where the handle is manipulated using wrist, elbow, and shoulder motions. However, these systems include only a few custom-made games.

To extend these systems, a cost-effective computer-based gaming platform has already been developed, which integrates various object manipulation tasks with engaging computer game activities. This platform uses a miniature, wireless, inertial-based (IB) computer mouse that directly connects object manipulation with digital gaming [19-22]. The IB mouse can be attached to a wide range of objects with different shapes, sizes, and weights and can be handled using 2-finger, 3-finger, or whole-hand motions as well as wrist, elbow, and shoulder movements. These object manipulation tasks are used to practice diverse, goal-oriented manual dexterity skills while users engage with entertaining computer games. However, this gaming system does not provide movement assistance for patients with limited active range of motion or poor movement control.

Numerous studies have assessed the feasibility and impact of various robotic systems aimed at improving UE functions in patients with stroke [23-30]. Augmented reality game–based devices focus on enhancing the range of motion in the shoulder, elbow, and wrist. However, these devices are not able to detect hand and finger movements with the required amount of precision. The camera-motion and sensor-based devices cannot detect movement with real-life objects. Thus, these devices can only detect active gross movements, neglecting object manipulation. A few robotic devices such as soft or hard gloves and exoskeletons do assist with finger and thumb flexion-extension; however, they primarily feature custom software applications that involve activities performed in digital settings rather than real object manipulations.

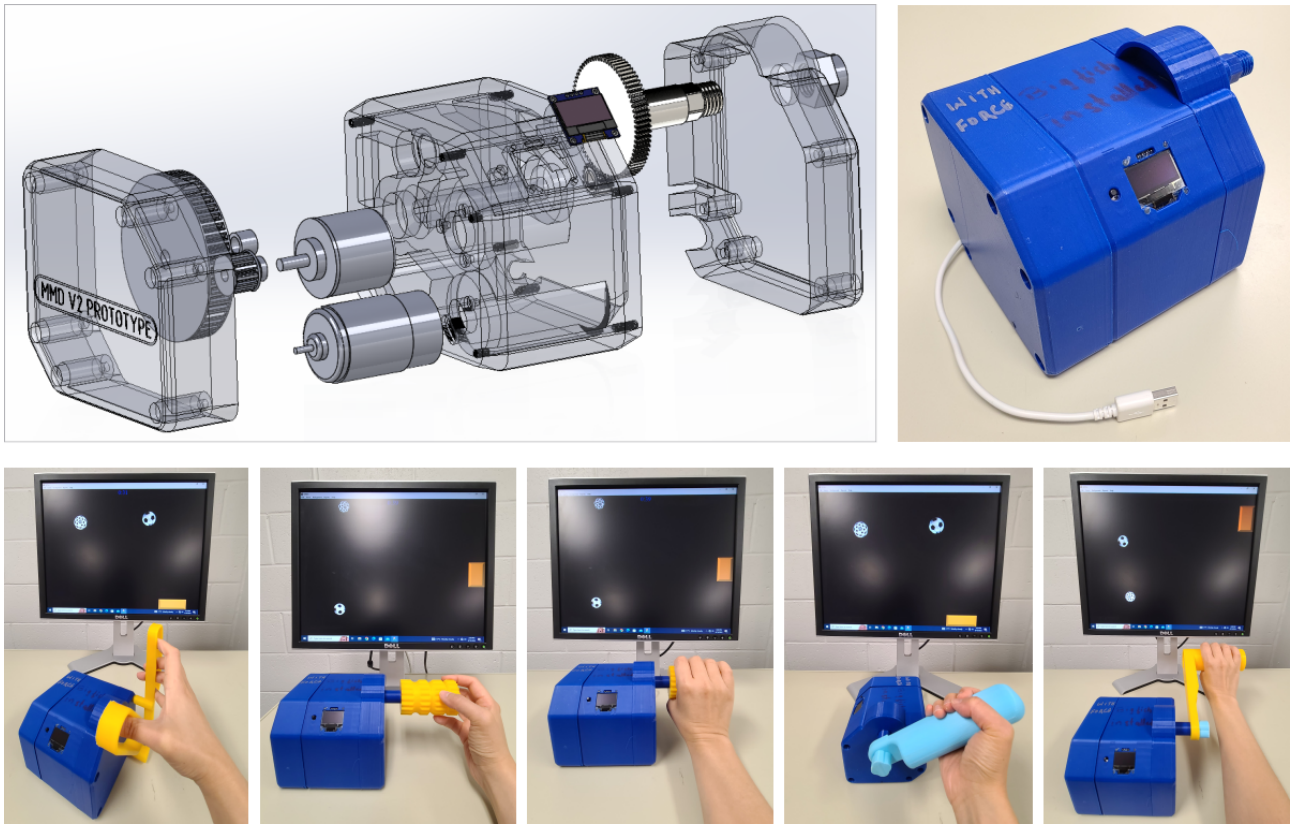
Given the above considerations, a low-cost, portable, multipurpose robotic manipulandum device (RMD) equipped with smart monitoring and assistive technologies for game-based rehabilitation of manual dexterity was developed. The RMD functions as a responsive, high-resolution computer mouse. In this paper, we first describe the RMD hardware and gaming software, its functionality, and related applications to provide both treatment and assessment of recovery programs targeting the manual dexterity of people after a stroke. The objective of this study is to present the results of a proof-of-principle pilot study conducted on 5 patients with stroke to examine the feasibility and benefits of a 6-week game-based exercise program using the RMD. The RMD described in this paper explains an integrated controller to generate forces that can aid voluntary movements necessary during gaming exercises, making it suitable for patients with limited movement control and those with a restricted active range of motion.

Description of the RMD and Software

Referring to Figure 1, the RMD features a compact, integrated 3D-printed chassis that contains the interface board, actuator, sensors, power train, and rotary drive shaft. Various 3D-printed therapy handles of different shapes and sizes can be attached to the shaft. These handles are designed to help users practice a wide range of manual dexterity skills involving thumb and finger movements as well as wrist, elbow, and shoulder functions. The RMD connects to a computer using a standard USB cable. An optical encoder tracks the shaft rotation, which corresponds to the movements of the handle and controls the motion of a computer cursor or game sprite in any single-axis computer game. In this context, the rotation of the shaft is mapped to pixel coordinates on the screen. An Arduino Leonardo microprocessor manages the RMD and its interaction with the games. Additionally, the RMD features a 3-cm LED display that shows several adjustable control parameters, which the user can modify:

- Gameplay orientation: mouse horizontal or vertical motion. Many common and modern video games are played with horizontal game sprite motion, but some require vertical motion.
- Working range: users can select an active range of motion for exercises, for example, from wrist neutral to 10, 20, or 30 degrees of extension or flexion ranges of motion, depending on individual patient needs, and map this to the full-screen mouse position.
- Mouse sensitivity: this setting determines the amount of movement required to navigate the mouse across the entire display range.
- Force: the RMD is designed to facilitate various assistive and resistive movement patterns. One of its applications involves a unidirectional force field mode, where a consistent force is exerted on the output shaft in a specific direction, with both the magnitude and direction adjustable. Many patients exhibit greater impairments in finger and wrist movement in 1 direction (eg, wrist extension), making the assistance of a constant force beneficial. Conversely, the opposite movement (eg, wrist flexion) can be met with a resistive force. This context-sensitive assistive or resistive mode can enhance even minimal voluntary movements in severely affected individuals, creating opportunities for progressive exercise that increases movement demands.

Figure 1. General view of the robotic manipulandum device and examples of various handles used for game-based rehabilitation of manual dexterity.



Since the RMD operates as a USB plug-and-play computer mouse, it is compatible with digitally any commercially available computer game. The inclusion of gaming elements motivates patients, providing an enjoyable way to engage in repetitive movements that are often necessary for rehabilitation. The therapeutic benefits from the types of object manipulation tasks involved vary in physical and anatomical requirements. The selected computer games provide graded responses in movement amplitude, speed, and precision. Table 1 outlines several common computer games that have been extensively tested with the RMD among patients of various ages. Additionally, a specially designed rehabilitation repetitive task practice (RTP) game has been created by the University of Manitoba and validated [31-33]. This simple game records the movements of the computer mouse curser or game paddle to assess the quality of movements. This game automatically tracks patients' goal-directed object manipulation tasks during both local and remote game–based therapy sessions, allowing for performance quantification in each session. This feedback can provide immediate results to the patient and help clinicians monitor progress over time. In practice, RMD-assisted exercises would initially use the RTP game software for therapeutic purposes. The RTP software is customizable, enabling adjustments to all game elements to suit the skill levels of patients with varying degrees of sensory-motor impairments.

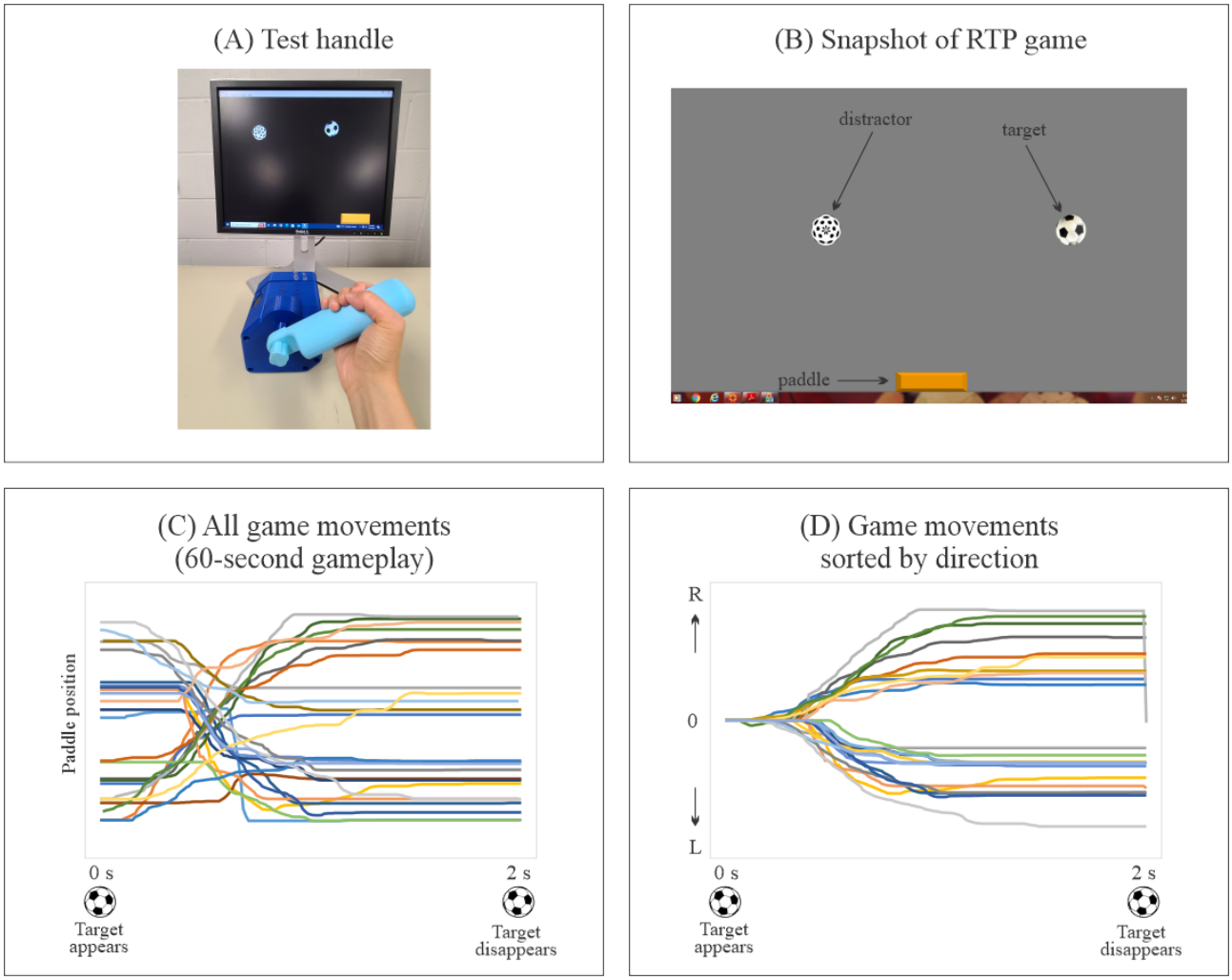
Table . Big Fish Games were used in this study [34].

Game	Axis play	Start difficulty	Response time	Clicker	Precision	Distractor	Type or activity
Abundante	Horizontal	Moderate	Self-paced (time limited)	Yes	Moderate	No	Color matching by directional aiming
Action Ball	Horizontal	Moderate	Fast	Yes	Moderate	Yes	Brick buster
Aqua Ball	Horizontal	Easy	Moderate	Yes	Moderate	Yes	Brick buster
Astro Bugz Revenge	Horizontal	Moderate	Slow	Yes	Moderate	No	Color matching by directional aiming
Birds Town	Horizontal	Moderate	Moderate	Yes	Moderate	No	Color matching by directional aiming
Brave Piglet	Vertical	Easy	Fast	Yes	Low	Yes	Shooting
Bricks of Egypt	Horizontal	Moderate	Fast	Yes	Moderate	Yes	Brick buster
Butterfly Escape	Horizontal	Moderate	Moderate	Yes	Moderate	No	Color matching by directional aiming
Egyptian Ball	Horizontal	Moderate	Fast	Yes	Moderate	Yes	Brick buster
Invadazoid	Horizontal	Moderate	Fast	Yes	Moderate	Yes	Brick buster
Jar of Marbles	Horizontal	Easy	Self-paced (time unlimited)	Yes	Moderate	No	Color matching by directional aiming
Jet Jumper	Horizontal	Difficult	Fast	Yes	High	Yes	Steering and jumping
Luxor HD	Horizontal	Moderate	Moderate	Yes	Moderate	No	Color matching by directional aiming
Ricochet Recharge	Horizontal	Moderate	Fast	Yes	Moderate	Yes	Brick buster

[a]Matching and shooting games require participants to use a small wireless optical computer mouse, pressing the left mouse button when needed. Precision is determined by the size of the paddle and the size of the target objects. Difficulty levels include game speed, the number of distractors, and matching choices.

Figure 2 illustrates a snapshot of the RTP game, highlighting game movement responses when using the RMD. Game objects appear randomly at the top of the display, moving at unpredictable speeds and directions toward the bottom. Players aim to maneuver the game paddle to catch these moving targets, with the RMD handle rotation controlling the paddle's motion. Distractor objects are included to increase challenge and can be toggled on or off. Configurable features include movement speed, precision (eg, sizes of game objects and paddles), movement amplitude, and the incorporation of distractors to assess the interplay between motor and cognitive processing as well as dual-task interference effects. Throughout gameplay, the RTP software logs the timing of each game object's appearance and disappearance, defining game events, along with tracking the position of the paddle and other game objects to establish movement context. Panels C and D in Figure 2 demonstrate typical movement trajectories within the game. Various performance metrics can be captured using the RTP game, offering immediate feedback for both patients and therapists. Additionally, electronic outcome measures are recorded to monitor progress and dose-response relationships in specific exercise programs over time, including success rates (SR), response times, movement durations, accuracy, and movement variability.

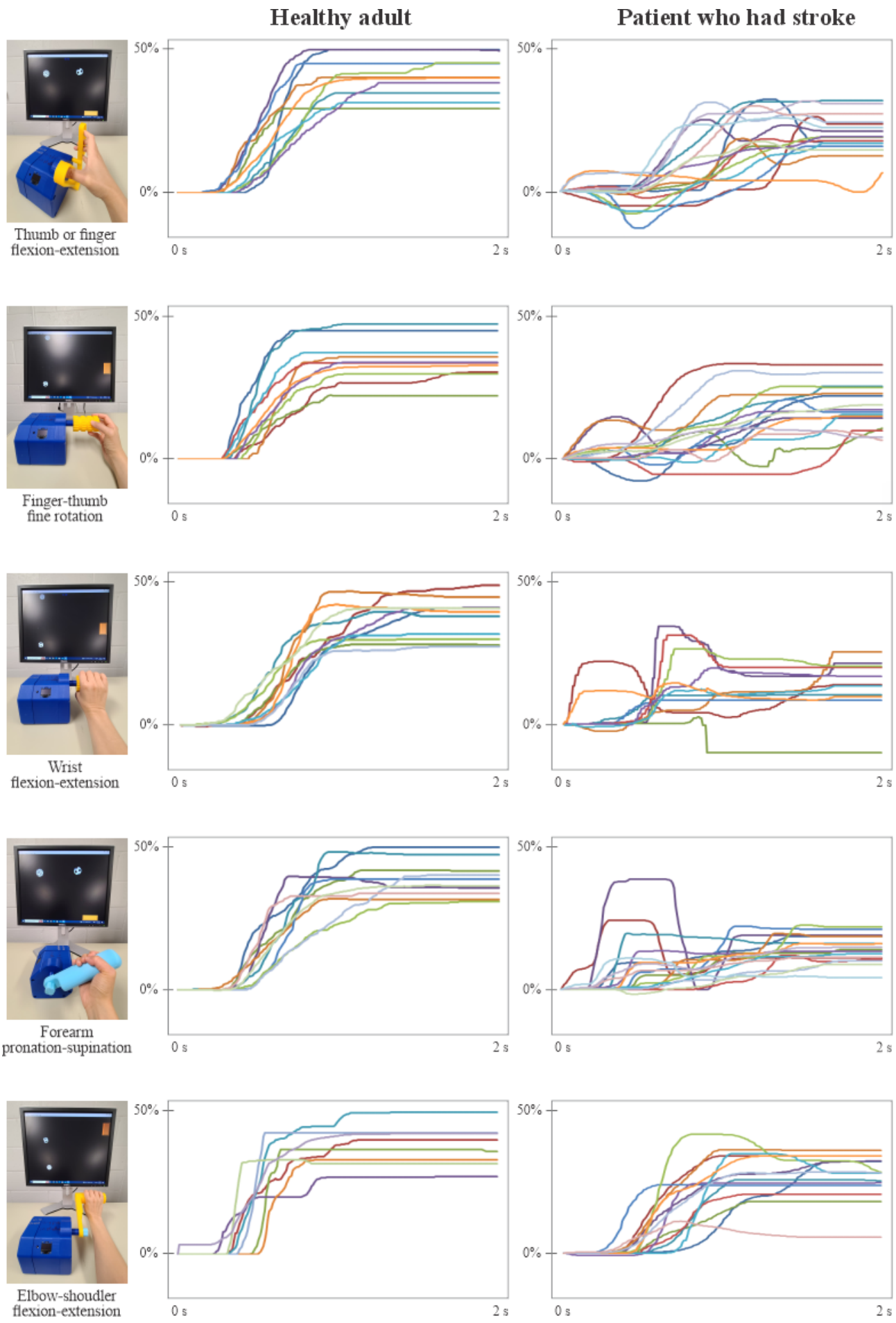
Figure 2. Illustration of RTP game software using the robotic manipulandum device. Panel (A) shows a healthy adult rotating a handle to move the game "paddle" and catch the "target" object while avoiding the "distractor" object. Panel (B) shows a screenshot of the game, where target and distractor objects appear at the top of the display and move to the bottom. Note that the addition of distractors is optional. Panel (C) presents single-game movement trajectories (game paddle coordinates) for all game movement responses in one session. In this example, each game event takes 2 seconds (from target appearance to disappearance), and the game is played for 60 seconds. The location of each successive target appearance is randomized. Approximately half of the 30 game events occur in each direction (leftward or rightward). Panel (D) presents overlay plots of the segmented and sorted game movement trajectories for all 30 game events; upward traces indicate leftward game movements, and downward traces indicate rightward game movements. RTP: repetitive task practice.



It is important to note that with standard commercial games, automatic performance logging is typically unavailable. Therefore, for any training sessions—particularly those conducted at home or remotely—the RTP game developed in-house serves as a valuable resource, providing automated monitoring and quantification of players' motor skills while engaging in a range of game-based exercises for hand and arm coordination (also referred to as telemonitoring).

Figure 3 presents game movement trajectories of a representative able-bodied adult and a patient with stroke playing the RTP game using various handles. As can be seen in the plots, the trajectories of the 5 different manipulation tasks are similar. The SR was 100% for all manipulation tasks. For the patient with stroke, the SR ranged from 50% (thumb-finger flexion-extension) to 80% (elbow flexion-extension). Movement consistency among the 10 - 12 game movement responses of the able-bodied adult was similar, as was movement onset time (MOT). Many of the movement trajectories of the patient with stroke were not smooth, exhibited small amplitudes, and demonstrated several target overshoots. It is also evident that the MOT is delayed in the participant with stroke compared to the able-bodied participant. It is, therefore, seen that the platform presented here is functional and can produce meaningful data for further analysis and treatment decisions.

Figure 3. Repetitive task practice game movement trajectories of an able-bodied adult and a patient with stroke using various robotic manipulandum device handles, as described in Figure 2. The plots show segmented and sorted game movement responses for 1 direction of movement. The y-axis represents movement amplitude as a percentage of screen width (0% to 50%).



Another key feature of the RMD and the associated RTP game software is that it is designed for use at home (telerehabilitation), not just in clinics. At present, the cost of the device is estimated to be less than US $70. The software automatically collects various objective outcome measures to monitor a patient's ongoing progress instantaneously and can be traced over a period of time. These data support the development of sustainable, individualized, long-term rehabilitation protocols. Furthermore, clinical support for home and remote outreach programs can facilitate the creation of more targeted and personalized solutions for patients.

The objective of this pilot study was to evaluate the implementation, usability, acceptability, and benefits of the game-based exercise program using the developed RMD presented in this paper. The experience of participants with stroke who completed a 6-week game-based exercise program was first assessed with semistructured interviews. Interviews were conducted to investigate participants' perspectives and opinions about expectations, acceptability, challenges, and benefits of the game-based exercise program for UE rehabilitation. Quantitative analysis pre- to postintervention was conducted next, which included the Wolf Motor Function Test (WMFT) and a computerized performance-based assessment of manual dexterity.

Methods

Recruitment

Participants were recruited at the clinical rehabilitation research facility of the University of Manitoba. In total, 5 individuals who had a single stroke (onset between 6 months and 5 years) and were aged 40 to 70 years participated in the study. All participants had adequate vision to see images on a standard computer monitor. Exclusion criteria were (1) excessive spasticity of the fingers and wrist (grade 2 and above on the Modified Ashworth Scale [35], (2) significant cognitive impairment (Montreal Cognitive Assessment scores less than 25 [36], and (3) any other neurological disorder except a single stroke before testing.

Ethical Considerations

The University of Manitoba Ethics Board reviewed and approved the study (approval HS25163), and all participants provided informed consent. The consent process ensured participants comprehended the study's objectives, procedures, potential risks, benefits, and their right to discontinue at any time. To maintain participant anonymity, all collected data were anonymized and stored in a secure, locked location. No compensation was provided, and no photographic or video recordings of participants were taken.

Exercise Program

Participants attended 12 treatment sessions twice a week for 6 weeks. Each session lasted 45 minutes. As shown in Figures 1 and 3, a variety of 3D-printed "therapy" handles of different shapes and sizes were used. They were designed to practice a broad range of manual dexterity skills. The exercise programs were established based on the participants' personal goals, the degree of their hemiparesis, and functional status. A typical session involved exercise with 4 to 5 different handles, several computer games, and assistive forces of different magnitudes. Each handle-game-force combination was practiced for 2- to 3-minute intervals and repeated 2 to 3 times. Different handles required different modes of manipulation. Game movement responses were produced by thumb, finger, wrist, or elbow movements. Task demands were adjusted by changing the mouse sensitivity movement range and by adding assistive-resistive forces. Additionally, different games were selected to adjust movement speed and precision. Most participants were competitive and became frustrated if they were not successful in gameplay. Therefore, the difficulty level (movement amplitude, speed, and precision) was adjusted for all combinations of handles, game settings, and game types so that participants were successful in gameplay for at least 60% of the game events or activities. Table 1 presents a list of common computer games used in this study. Big Fish Games are selected based on the level of difficulty participants reported and their personal likes and dislikes. The choices of games presented to them were based on columns 3 to 7 of Table 1. Games with an easy level of difficulty (based on the level of precision required, the presence of distractors, and the type of executive functions required) were introduced before the moderate and difficult games. Task difficulty was also adjusted by increasing the assistive and resistive forces applied to the RMD handles.

The exercises and choice of games were updated on a regular basis, based on the participants' improvements and personal preferences for game selection. Numerous affordable and readily accessible computer video games offer therapeutic benefits. For instance, computer games downloaded from Big Fish Games feature hundreds of arcade-style games across various genres (Table 1). Many of these games align well with the game-based RMD exercise program. In addition to requiring speed and accuracy, these games incorporate several cognitive elements, such as speed versus accuracy dynamics, distractor objects, and object-matching activities. The commercial computer games used in this pilot study are listed in Table 1. The wide variety of games ensures that the individual preferences of participants can be fulfilled. Regularly introducing new games and increasing the difficulty levels can help maintain the challenge, providing the psychological feedback necessary to keep participants engaged and motivated.

Qualitative Analysis

At the end of the 6-week exercise program, all participants were invited to participate in an interview. They were asked a series of open-ended questions, and their responses were documented: (1) when you agreed to participate, how did you hope you would benefit from the therapy program? (2) Were there things about the game or exercise program you liked and things you did not like? (3) What did you think about the computer games that you were asked to play? Did you enjoy the game? Were there games that you did not enjoy? (4) Did you feel that this therapy program helped you? (5) If you were provided with the right settings, would you continue with these exercises?

The duration of the interviews varied among the 5 participants, lasting between 20 and 30 minutes. Participants were invited to share their thoughts, ideas, opinions, and personal experiences

in detail. The analytical framework of interpretive description was used for thematic analysis [37]. All interviews were recorded, and the interviewer's notes and comments were added to the transcriptions separately for triangulation purposes. One researcher (AK) reviewed the translated transcripts and created a coding system, while a second researcher (TJS) oversaw the process and added any additional codes for credibility purposes. A second researcher (TJS) then examined the coded data to identify any unique responses.

The content of each interview was analyzed by paraphrasing, generalizing, and abstracting. A continuous iterative process was maintained until no new themes emerged from the data. The 2 researchers then compared their analyses and resolved any disagreements in a final coding system organized into final themes and subthemes.

Quantitative Analysis

Overview

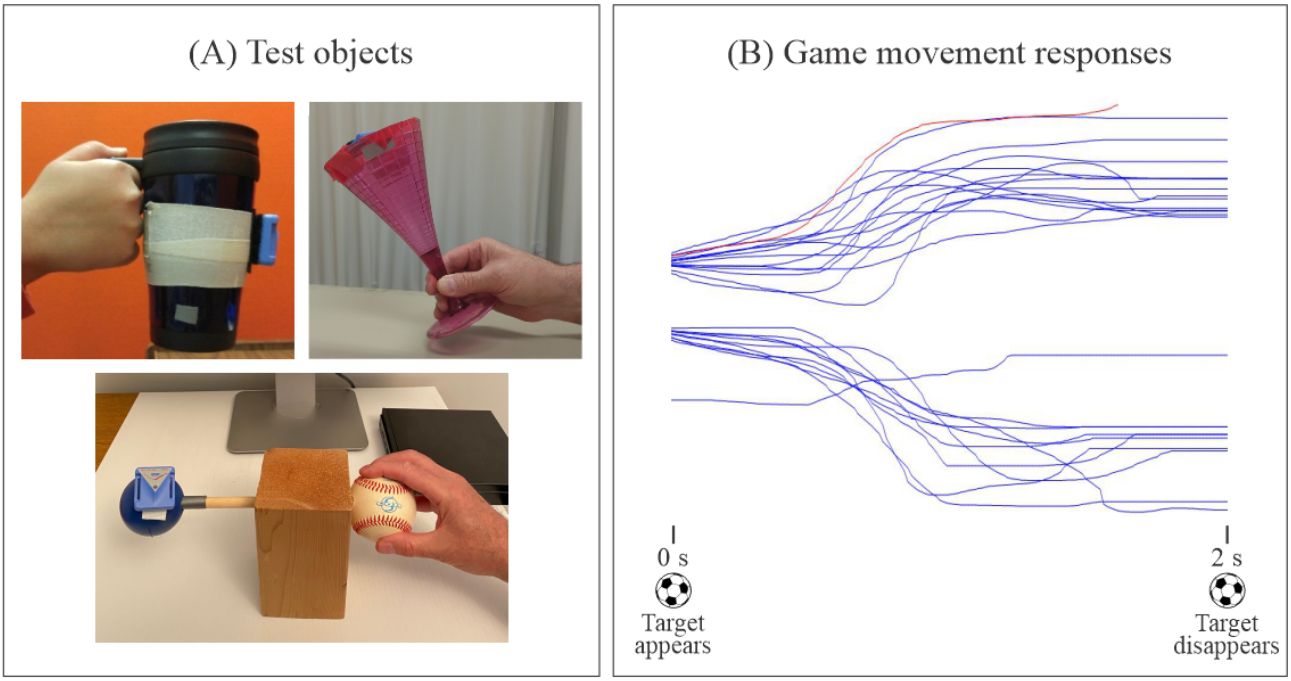
The following outcome measures were obtained before and after the intervention of the 6-week exercise program:

1. Quantitative assessments of UE motor ability were conducted using the WMFT [38,39]. Participants were instructed to complete the 15 tasks of the WMFT within a 120-second time limit, and the time taken to complete each task was recorded. Additionally, the quality of movement for each task was evaluated using an ordinal scale ranging from 0 to 5, where 0 indicates no performance and 5 indicates normal movement. The final WMFT scores were the total time taken for the 15 tasks and the summed movement quality grades of the 15 tasks.
2. The RTP game was used to guide and evaluate different object manipulation tasks. In this application, several test objects with different physical properties and anatomical demands were instrumented with a wireless IB mouse. The rotation of each test object (ie, the instantaneous angular position of the IB mouse) controlled the motion of the game paddle. For a detailed description of the assessment tool, see references [20,33]. All tasks required precision in object manipulation using the finger-thumb or hand palmar surface.

Test Objects

In the context of the RTP game assessment, the following test object manipulation tasks were evaluated, as illustrated in Figure 4: (1) participants grasped a coffee mug to move it with concentric pronation and eccentric supination. (2) Participants held a wine glass between the thumb, index, and middle fingers. It was rotated forward and backward using radial and ulnar deviation. (3) Participants grasped a tennis ball with the thumb and fingertips tethered to a wooden block via a wooden dowel to eliminate the gravity effect. This task required the participant to rotate the tennis ball left and right.

Figure 4. Illustration of the computer game–based upper extremity assessment tool. (A) Three test objects, each equipped with an inertial-based mouse, were used to control the repetitive task practice game paddle movements. (B) Example overlay plots of the segmented and sorted game movement responses for both movement directions: pronation-supination using a coffee mug, ulnar-radial deviation using a wine glass, and leftward-rightward rotation using a tennis ball.



The assessment presented here allows one to determine if there is a transfer of improvement in manual dexterity with objects used in daily life. Moderate to high test-retest reliability of the assessment tool has been reported in a group of 30 patients with stroke [20] and a group of 35 children with cerebral palsy [21].

Test Protocol

Participants were seated with test objects positioned within a comfortable reaching distance on an adjustable-height table. A 50-cm wide computer monitor was placed 1 m in front of them at eye level to perform the assessment game tasks. Participants received a demonstration of the game tasks and were allowed

to practice trials using their unaffected arms. Figure 4 presents typical overlay plots of game movement trajectories for both movement directions for 1 game session.

Outcome Measures

The following outcome measures were derived from the recorded game data of the assessments: SR and average MOT. The percentage of the total number of target objects caught in 1 game trial is the SR. The time from target appearance to the start of the game paddle movement is the average MOT. MOT values are determined for each game movement response. The average is then computed over the group of game movement responses for each direction.

Results

Participants

Table 2 presents the demographic and clinical data of the 5 participants. All participants, who experienced a single stroke, agreed to take part in the study and provided informed consent. They were all right-handed and fully completed the 6-week program, which included 2 exercise sessions per week, each lasting at least 45 minutes.

Table . Demographic and clinical characteristics of participants.

Participant	Age (years)	Sex	Type of stroke	Duration (months)	Affected side	Hand dominance
Participant 1	67	Male	Ischemic	24	Left	Right
Participant 2	68	Male	Ischemic	16	Left	Right
Participant 3	57	Male	Ischemic	12	Left	Right
Participant 4	43	Female	Ischemic	4	Left	Right
Participant 5	51	Male	Hemorrhagic	56	Left	Right

Qualitative Results

The following 4 themes capture the range of participants' experiences and viewpoints regarding the prototyped RMD exercise program: expectations, difficulties with technology, engagement with therapy, and future expectations. Table 3 presents examples of participants' direct quotes for each interview question (theme).

Table . Typical participant responses to interview questions.

Theme	Response
Expectations	• "I get into problems while handling day-to-day things. I often have trouble gauging how much distance and pressure I need. The other day I squeezed the soda cup too hard and spilled everywhere. I am hoping to improve the finer aspects" [Participant 1]. • "My consultant physician told us that I was never going to use my fingers. When we heard about this program, we thought it might help" [Participant 3].
Difficulties with technology	• "Learning how to use the RMD was hard at first. Learning how to move the mouse when my arm is so restricted, you know?" [Participant 3]. • "I am not a tech-savvy person. It took a while to get used to the games and the robot (RMD)" [Participant 4]. • "Coming to therapy twice a week and getting a ride in winter was a lot. But the home-based therapy was not working, so we decided to do it" [Participant 5].
Engagement with therapy	• "I am very competitive. I like that the computer games challenged me. It was fun" [Participant 1]. • "It (conventional therapy) did not show much improvement. It did not seem like it was worth the trouble. I wanted to check out this option (computer games-based protocol) because it sounded new, something fun" [Participant 4]. • "I could comb my hair again. That was something!" [Participant 2]. • "My hand felt completely immobile earlier; now I can use it to support my other hand for different tasks" [Participant 3]. • "I was happy to see that you guys created a steering wheel handle for me to relearn driving" [Participant 5].
Future expectations	• "Honestly, I think we could have done this from home if you had enough of these (RMDs). We can just download these games on my laptop" [Participant 5].

Expectations

All participants indicated that the primary reason for their participation in this exercise program was to improve their hand function, particularly in handling and manipulating objects. One participant agreed to participate because his therapist recommended the program. It is noteworthy that it had been several weeks to over 3 years since the participants last received physiotherapy or occupational therapy.

Difficulties With Technology

In total, 3 of the 5 participants reported that they had not played computer games before. However, they noted that the games were easy to learn. All participants found it intuitive to use the RMD as a game controller. They all considered the exercise program challenging and expressed that it was difficult to play the games by manipulating the RMD handle. Nevertheless, with practice, the exercises became significantly easier. All participants exhibited competitiveness and experienced frustration when they could not successfully play the games. This was taken into account, and the games were carefully selected to match the skill levels of each participant.

Engagement With Therapy

All participants stated that they had previously undergone physiotherapy and occupational therapy for several weeks. They expressed appreciation for the one-to-one therapy sessions, noting that receiving immediate feedback and guidance from the therapist was very helpful. Participants also reported that it was beneficial to know which games to use and why. They indicated a preference for certain games and appreciated the variety available to them during therapy. Furthermore, all participants commented that it was more enjoyable and easier to perform game-based exercises than conventional exercises.

Future Expectations

All participants expressed a desire to continue the program and inquired whether it would be possible to use the device at home.

Quantitative Results

Table 4 presents the pre- and postintervention test scores for the WMFT, highlighting the changes observed from pre- to postintervention. In patients with stroke, the minimal clinically important difference (MCID) for the functional ability score has been reported to range from 3 to 6 points, while the MCID for the total time of the WMFT is 22 seconds [40]. All 5 participants in this study demonstrated postintervention improvements that exceeded the reported MCID for the functional ability measure (with a range of improvement between 9 and 16 points). In total, 4 of the 5 participants exhibited improvements in total time that surpassed the MCID (with a range of improvement between 23 and 28 seconds).

Table . Pre- and postexercise Wolf Motor Function Test scores and magnitude of change.

Participant	Functional ability score (maximum: 75)			Total time (seconds)		
	Pre	Post	Change	Pre	Post	Change
Participant 1	19	28	9	119	71	48
Participant 2	19	34	15	118	84	34
Participant 3	13	27	14	73	62	11
Participant 4	12	28	16	104	71	33
Participant 5	9	23	14	89	65	24
Average (SD)	14 (4)	28 (4)	14 (3)	101 (20)	71 (8)	30 (14)

Figure 5 displays example plots of game movement responses using the 3 test objects, recorded at baseline and after the completion of the 6-week exercise program from different participants. Visual inspection reveals a clear improvement in movement quality, amplitude, and consistency. As indicated in Table 5, substantial improvements were observed in SR and response time for all 5 patients. For SR, the average improvement was 23% (SD 12%), while for response time, there was an average decrease of 105 (SD 44) milliseconds. It is noteworthy that typical response times were approximately 600 milliseconds.

Figure 5. Examples of repetitive task practice game movement responses (1 direction) from different participants using the 3 assessment test objects, taken at pre- and postintervention time periods.

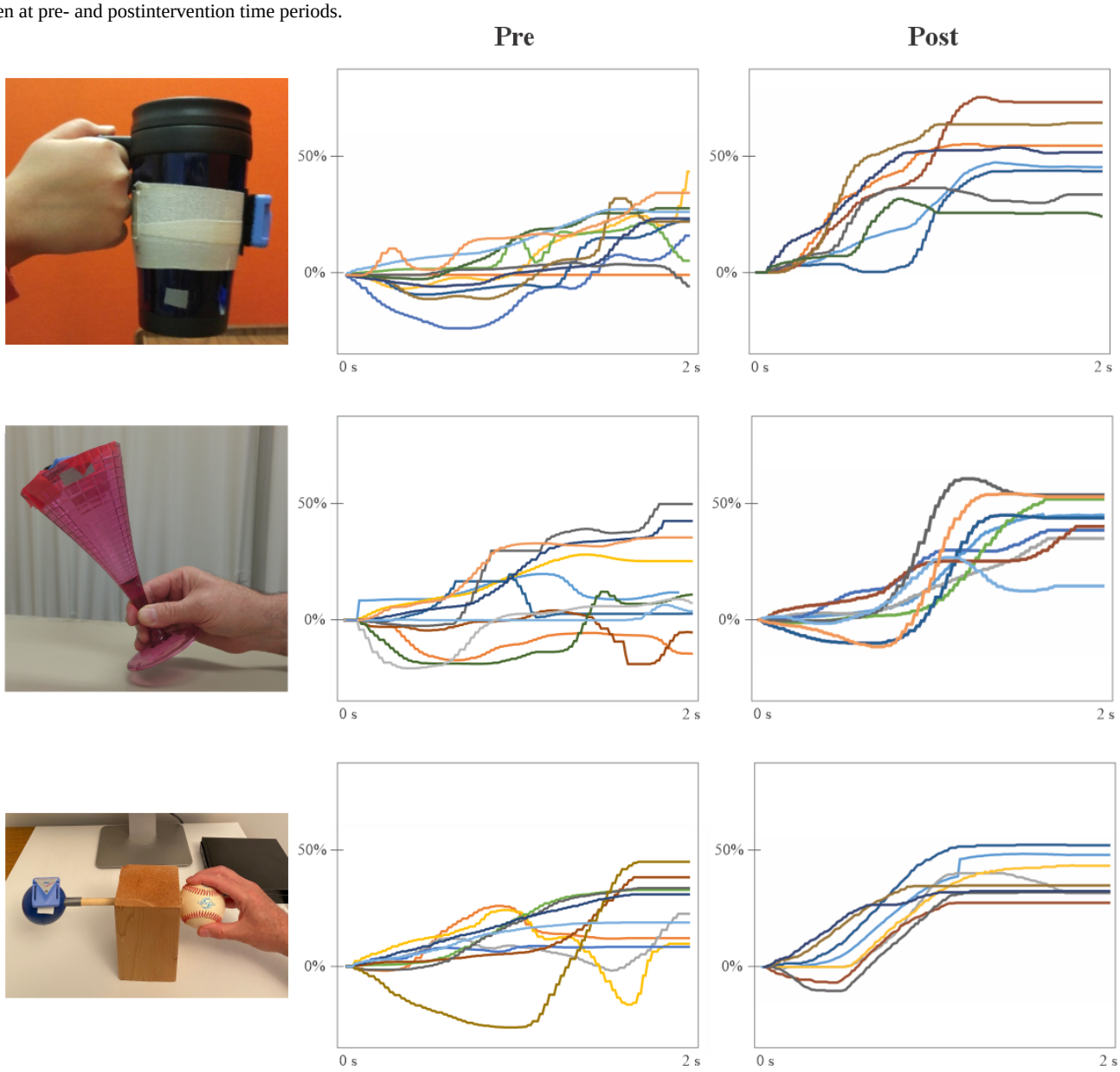


Table . Pre- and postexercise test scores and magnitude change of object manipulation tasks for all participants[a].

Participant and test object		Success rate (%)			Response time (milliseconds)		
		Pre	Post	Change	Pre	Post	Change
Participant 1							
	Object 1	42	91	49	723	530	193
	Object 2	65	89	24	478	423	55
	Object 3	51	68	17	792	697	95
	Average (SD)	53 (12)	83 (13)	30 (17)	664 (165)	550 (138)	114 (71)
Participant 2							
	Object 1	50	100	50	528	532	−4
	Object 2	54	62	8	780	702	78
	Object 3	33	100	67	771	421	350
	Average (SD)	46 (11)	87 (22)	42 (30)	693 (143)	552 (142)	141 (185)
Participant 3							
	Object 1	42	64	22	845	811	34
	Object 2	70	75	5	845	771	74
	Object 3	61	73	12	794	805	−11
	Average (SD)	58 (14)	71 (6)	13 (9)	828 (29)	796 (22)	32 (43)
Participant 4							
	Object 1	54	85	31	576	490	86
	Object 2	50	55	5	786.	515	271
	Object 3	66	80	14	784	725	59
	Average (SD)	57 (8)	73 (16)	17 (13)	715 (121)	577 (129)	139 (115)
Participant 5							
	Object 1	66	78	12	823	783	40
	Object 2	72	92	20	806	588	218
	Object 3	56	72	16	760	722	38
	Average (SD)	65 (8)	81 (10)	16 (4)	796 (33)	698 (100)	99 (103)

[a]Values are the average of left and right game movements. Object 1: coffee mug; object 2: wine glass; and object 3: tennis ball (Figure 5).

Discussion

Principal Findings

This paper introduced a rehabilitation device that provides flexible, game-based RTP targeting manual dexterity and includes means to automatically record and assess patients' manual dexterity skills using the RTP software. The 6-week exercise program resulted in clinically significant improvement. In terms of the WMFT, on average, participants showed an improvement of 14 (SD 3) points in functional ability score and a reduction of 30 (SD 14) seconds in total time. Additionally, for the computer game–based UE assessment, the average improvement in success rate was 23% (SD 12%), while the average decrease in response time was 105 (SD 44) milliseconds. The proposed system not only addresses patients' exercise needs but also integrates enjoyment and learning through a gaming platform.

The change in WMFT scores exceeded the MCID for all participants. The WMFT measures daily activities involving fingers, such as picking up small objects and using hand tools. Significant improvements in the WMFT were observed, even though these specific tasks were not practiced during the game-based manipulation program. The WMFT also assesses visual perceptual skills for tasks like stacking blocks and drawing figures. The RMD game tasks, which require precision movements based on visual feedback, showed substantial improvements in both the WMFT tasks and object manipulation tasks in the RTP game. Participants with stroke noted that the game-based exercises were challenging yet engaging and enjoyable.

Handles of different sizes and shapes were used to target precision, goal-directed movements of the thumb, fingers, and wrist as well as combinations of UE movements. In addition to the types of handles used, computer games also possess therapeutic value. Different commercial video games require varying levels of movement speed, accuracy, and amplitude.

For example, participants with severe impairments were able to successfully play computer games when the selected games involved slow movements and low precision (ie, large game paddles and target game objects). Participants with moderate to mild impairments could engage with computer games that required faster speeds and greater precision.

The games also involved various executive cognitive functions, including visual search and spatial processing of moving targets and distractors. The diverse range of games and regular updates to difficulty levels are important for maintaining engagement and challenge.

The RMD is configured to function exactly as a plug-and-play computer mouse and, therefore, can be used to play many commercial computer games. This allows easy access to a large source of commercial games. To meet the needs of each individual, the RMD can be customized to suit specific rehabilitation needs and preferences. This adaptability allows patients to engage with a variety of gaming experiences tailored to their specific motor and cognitive rehabilitation goals. A key feature of the program is to increase the number of repetitions of goal-directed movements at varying speeds and accuracy levels. High intensity and a high number of repetitions are crucial to drive neuroplasticity and functional improvement in patients with stroke [41-45].

Each game-handle combination was played for 3 to 5 minutes, and typically, each game event took approximately 2 seconds. Therefore, participants made 90 to 150 goal-directed game movement responses during this time period. Each session lasted 45 minutes and included 7 to 8 different handles, resulting in several hundred game-handle combinations. The goal-directed game movement responses varied in amplitude, speed, and direction. During gameplay, visual feedback of the game sprite or paddle relative to the game target and distractor objects was used to initiate and guide each contextual game movement response, supporting implicit learning of eye-hand coordination. Additionally, the selected video games featured unpredictable trajectories for game target motion, promoting variable practice.

Interestingly, significant improvements were observed in a participant who was 5 years after a stroke, which was unexpected given that most studies include participants less than 2 years after a stroke. Although some studies have reported significant improvements in UE function 3 to 5 years after a stroke, this finding is based on only 1 participant. Future randomized controlled trials are needed to examine the effectiveness of game-based task-specific exercises for participants 3 to 5 years after a stroke.

Recovery programs can be extensive, involving RTP for many months. A key feature of the RMD is its design for home use (telerehabilitation). In this regard, the cost of the electronic components, motor housing, and handles is less than US $70. Additional costs, several times this amount, will likely be required for the commercialization of the RMD system. The RMD can initially be used in a supervised clinical setting and then transitioned to home use while being monitored by clinicians. The telemonitoring capabilities of the system (ie, RTP game) could allow clinicians to track changes in function and compliance, facilitating the development of sustainable and individualized programs. Prompt clinical assistance for home and remote outreach programs will foster more tailored and effective solutions for patients, facilitating the intended training outcomes. This will require further development to produce a secure content management system for individual electronic game data to be updated and stored for processing as well as to generate queries and reports for registered eHealth stakeholders (eg, therapists, physicians, and third-party insurance providers).

Limitations

The unidirectional force mode, while assisting movement in 1 direction, results in resistance forces in the opposite direction, which may not be desirable. A real-time intelligent control scheme is under development, involving communication between the RMD software and the RTP game. In the upcoming system, the controller will receive coordinates for both the game targets and the paddle, which is controlled by handle rotations. This information about movement directions and amplitudes can then be used. The system will determine the direction and magnitude of the force necessary to rotate the handles effectively to move the game paddle within the RTP game. Notably, this closed-loop assistance can be offered in both movement directions during gameplay. This context-sensitive assistive mode helps facilitate limited voluntary movements in severely affected individuals.

Conclusions

The results of the pilot study indicate the feasibility, acceptability, and positive outcomes of the RMD game–based system for enhancing manual dexterity in people with stroke who have moderate UE motor impairments. The intervention resulted in clinically significant improvements, with all participants showing enhanced performance in the WMFT beyond the MCID. These findings suggest that the system has the potential to advance rehabilitation treatments for finger, thumb, and wrist recovery in people with stroke. The long-term effects of this training on manual dexterity will need to be evaluated in future randomized controlled trials. However, the current findings are encouraging and provide a strong basis for further research and development.

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Conflicts of Interest

None declared.

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Abbreviations

IB: inertial-based
MCID: minimal clinically important difference
MOT: movement onset time
RMD: robotic manipulandum device
RTP: repetitive task practice
SR: success rate
UE: upper extremity
WMFT: Wolf Motor Function Test

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Poststroke Neurorehabilitation Using a Soft Robotic Glove Combined With a Virtual Environment: Preliminary Study on Feasibility, Safety, Effects, and User Satisfaction

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Abstract

Background: Optimizing rehabilitation intensity using a robotic-assisted hand rehabilitation exercise (RAHRE) program coupled with a virtual environment is a promising intervention as it aligns with key neuroplasticity principles.

Objective: The aim of the study is to assess the feasibility, safety, preliminary effects, and satisfaction of the 2-week RAHRE program offered as an adjunct to conventional rehabilitation.

Methods: In total, 11 adults with hand hemiparesis following a recent stroke and undergoing intensive functional rehabilitation were randomized into experimental and control groups. Both groups received conventional rehabilitation therapy over a 2-week period. The experimental group received 10 additional 30-minute sessions of the RAHRE program (5 times per week), incorporating 4 hand opening and closing exercises with personalized glove assistance or resistance levels with virtual reality over the same period. Measures of feasibility (ie, attendance rate, compliance rate, repetitions per session, active training time, therapist verbal cueing, and support required), safety (ie, discomfort and adverse effects), and satisfaction (ie, satisfaction questionnaire) were collected. Functional outcomes (ie, Action Research Arm Test [ARAT], Fugl-Meyer Assessment for the Upper Extremity [FMA-UE], Box and Block Test, ABILHAND) were also assessed before and after the intervention in both groups.

Results: Attendance and compliance rates in the experimental group reached 96% (48 completed training sessions of 50 planned sessions) and 95% (1432 completed training minutes of 1500 planned minutes), respectively. Participants performed a median of 2543 (IQR 2368-2951) additional movement repetitions during the RAHRE program (median repetitions per session 260, IQR 173-365; median active training time 24 minutes 39 seconds, IQR 22 minutes 26 seconds-25 minutes 51 seconds). Minimal therapist verbal cueing and support were necessary for technology use (median glove donning time 46, IQR 27-60 seconds; median independence achieved in 6, IQR 4-7 sessions). No abnormal discomfort or adverse effects were reported. Both groups showed functional improvements in ARAT, FMA-UE, Box and Block Test, and ABILHAND. For the primary outcomes (ie, ARAT and FMA-UE), the median score changes were, respectively, 4.50 (IQR 0-9) and 4.00 (IQR 3-4) in the control group, and 4.00 (IQR 1-7.5) and 5.00 (IQR 5-6) in the experimental group. Excellent overall program satisfaction (median 5/5, IQR 5-5) was reported for the RAHRE program.

Conclusions: The RAHRE program, as an adjunct to conventional rehabilitation therapy, emerges as being feasible, safe, beneficial, and satisfying for adults with hand hemiparesis following a recent stroke. However, careful interpretation of the results remains recommended given the strength of the evidence. Future studies providing higher-quality evidence are needed.

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KEYWORDS

exercise; exoskeleton device; hand recovery; rehabilitation; robotic glove; stroke; virtual reality

Introduction

Despite intensive functional rehabilitation efforts, 75% of people who sustained a stroke continue to experience difficulties with hand sensorimotor impairments beyond 3 months after stroke, which negatively affect their participation in daily activities [1]. To enhance poststroke recovery, evidence suggests combining various treatment modalities (eg, constraint-induced therapy, mirror therapy, robotics, and virtual reality) that integrate principles of neuroplasticity into a rehabilitation intervention [2,3]. The principles of neuroplasticity emphasize the benefits of high-intensity activity-based therapy soon after stroke [4]. However, clinical settings face challenges in achieving these high-intensity goals due to administrative constraints such as high caseloads and limited therapist availability [5]. Emerging technologies, notably robotic gloves, offer potential for integrating diverse treatment modalities into a single intervention, thereby both intensifying and enhancing rehabilitation opportunities while simultaneously alleviating any clinical or administrative burdens.

Over the past 50 years, robotic gloves have emerged as valuable assets in both clinical and research settings for promoting upper extremity function and recovery, particularly when provided for the duration of at least 30 minutes daily over a minimum period of 2 weeks [6]. These gloves can assist movement and provide haptic feedback with realistic proprioception and tactile sensations, which may improve dexterity and fine motor skills. Combining the use of a robotic glove with virtual reality represents a multimodal approach that enhances various forms of sensory feedback [7]. Beyond the rehabilitation benefits of the gloves themselves, augmented visual and auditory feedback can be provided via realistic and appealing interactive virtual reality environments created for specific motor training tasks, thereby boosting the engagement and motivation of individuals with stroke in pursuing their neurorehabilitation [8].

Advancements in glove technology have progressed, with some now available commercially, offering features tailored for rehabilitation settings such as movement tracking, kinesthetic and tactile feedback, and compatibility with virtual reality environments [9]. Recognizing the potential of these features, the Dexmo glove, a commercialized robotic glove (DextaRobotics), was selected to be coupled with our newly developed virtual environment software platform, btrained (version 2.0), specifically designed for hand rehabilitation after a stroke [10]. This coupling is now ready for clinical testing in the form of a robotic-assisted hand rehabilitation exercise (RAHRE) program to complement and intensify conventional hand rehabilitation and is the focus of this feasibility study.

This study aims to assess the feasibility, safety, and preliminary effects on hand-related functional abilities while also assessing satisfaction of a novel 2-week RAHRE program offered as an adjunct to conventional rehabilitation. Recruitment, attendance and dropout rates, learnability, and the progression of dosage over the course of the program were measured to determine the feasibility; presence of participant-specific undesirable effects such as discomfort, pain, spasticity, and skin and soft tissue integrity or the occurrence of any other adverse effects were measured to determine safety; and functional outcomes were measured to determine the effects of the program. Moreover, a questionnaire of participants' satisfaction toward the program was completed to determine satisfaction. The study hypothesis was that the RAHRE program is feasible and can safely intensify conventional hand therapy while inducing beneficial functional changes and satisfaction for participants. It is anticipated that the findings will enrich and inform a future larger-scale efficacy study.

Methods

Study Design

A prospective intervention feasibility study with pre- and postevaluations was carried out over a 6-month period to assess the 2-week RAHRE program. As this was a feasibility study, no a priori power analysis was performed to determine the sample size. Participants were randomly allocated to an experimental group (RAHRE program) or a control group (conventional rehabilitation therapy) through a block randomization method. This process was facilitated by a computer-generated algorithm to ensure unbiased allocation. The randomization was centrally managed by a single designated research team member (DHG) who was not involved in the assessment or in the intervention. The use of block randomization improved the chance of maintaining balanced group sizes and minimized selection bias throughout the study. A preintervention evaluation was completed prior to group allocation, and a postintervention evaluation was completed within 40 hours upon completion of the RAHRE program. The initial evaluation included a familiarization period for all participants to acquaint themselves with the technology, ensuring that no additional exclusion criteria could hinder its use if assigned to the experimental group.

Participants Recruitment

A nonprobabilistic consecutive sample of 11 adults who sustained a stroke and were undergoing an inpatient intensive functional neurorehabilitation program offered by a publicly funded rehabilitation center was recruited. Participants had to meet the following eligibility criteria: have hand sensorimotor impairments and functional disabilities, as determined using the subscale of the hand subsection of the Fugl-Meyer Assessment for the Upper Extremity (FMA-UE; FMA-Hand<14). Exclusion criteria included a lack of minimal motor recovery using the earlier-mentioned subscale (Dexmo glove requirement of FMA-Hand ≥1) or the inability to provide consent, to communicate in French, English, or Spanish, or to understand simple commands. All patients admitted to the rehabilitation center between September 15, 2023, and March 15, 2024, and meeting inclusion criteria were identified by a clinical research coordinator (Frédéric Messier) who communicated with their assigned occupational therapists for screening. If the patient was deemed eligible, a research professional explained the research project, verified interest in participating, and invited the person to sign the consent form.

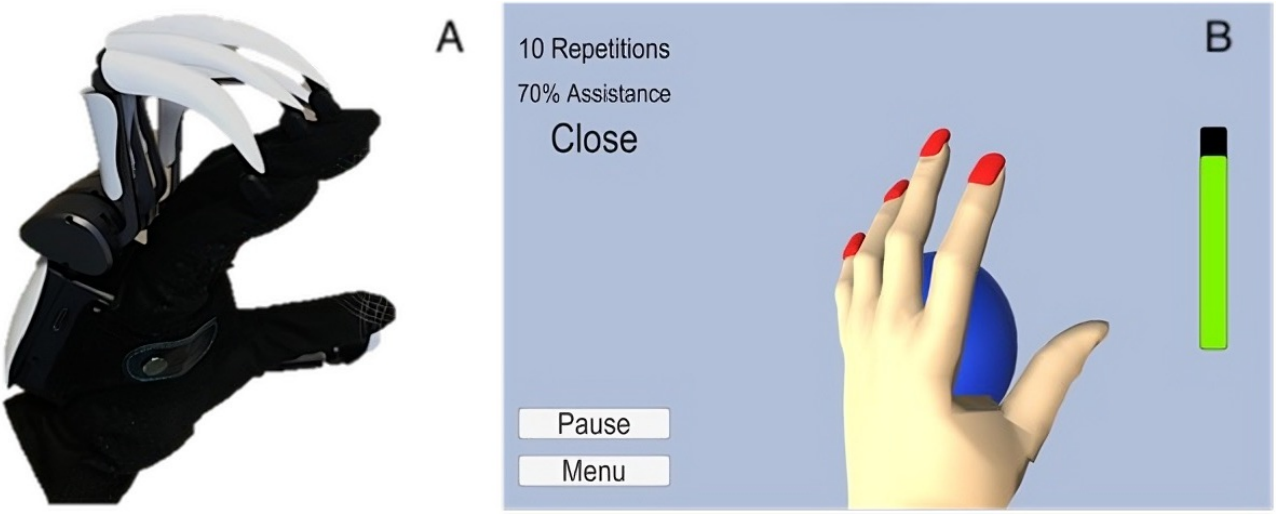
Ethical Considerations

The project was approved by the Rehabilitation and Physical Disability Research Ethics Committee of the Centre Intégré Universitaire de Santé et de Services Sociaux Centre-Sud-de-l'Île-de-Montréal (2023 - 1822). All participants provided written informed consent prior to participation. Participant data were anonymized to ensure privacy and confidentiality. Participants received approximately US $14.56 per evaluation visit (2 visits in total) as compensation for their time and any inconvenience, as outlined in the consent form.

Soft Robotic Glove and Software

Although defined hereunder as a robotic glove, the Dexmo can be classified as a wearable hand exoskeleton or exoglove. The Dexmo enables 11 degrees of freedom of hand motion (flexion or extension and abduction or adduction of all 5 fingers and additional rotation for the thumb). It is worn on the dorsal side of the hand, and each finger is connected to the main controller at the end effector using a cloth glove (Figure 1A). The Dexmo includes a sensory module for detecting finger movements and an actuation module for adjusting force transmission to assist with movement execution [11]. The glove is linked to a virtual environment software, btrained (version 2.0), that reproduces the hand and its movements in real time through an avatar using 3D graphics.

Figure 1. The robotic glove and software. (A) Dexmo glove. (B) Exercise level 1 in the virtual environment on btrained (version 2.0) software.



The btrained (version 2.0) software, developed in partnership with Canada's National Research Council using Unity software (Unity Technologies), evolved from previous iterations to address the needs of people who sustained a stroke [10]. A session with btrained (version 2.0) begins with a 1-time glove calibration for avatar movement mirroring. The session continues by having participants explore the 4 developed hand exercises associated with a spherical grip. The first level involves hand opening and closing exercises over a static 45-mm diameter virtual ball (Figure 1B). Throughout this level, glove assistance decreases by 5% for every 3 repetitions of full-finger movement, starting from 100% assistance (equivalent to ~1.8 N) and ending with 0% assistance, then increasing by 5% in resistance up to 100% resistance (equivalent to ~7 N). Exercise level 2 consists of a 10-minute hand opening and closing exercise with constant assistance or resistance. Exercise level 3 involves the same hand opening and closing exercise but requires the participant to follow a constant tempo (0.33 Hz) set by a metronome for the duration of 10 minutes. Exercise level 4 is similar to exercise level 3 but with a metronome tempo that increases with the number of repetitions. Visual and congruent auditory feedback signals to the participant whether or not the movement is synchronized with the metronome tempo.

At the start of each session, participants only have access to exercise level 1. Completing this level allows the software to automatically personalize the difficulty threshold for subsequent exercises (ie, levels 2, 3, and 4) to be 10% easier than level 1. Once level 1 is completed, participants have full access to the other exercises for the remainder of the 30-minute session, allowing them the freedom to choose the order and duration of each exercise. At any point during any exercise, participants can pause or end the exercise using the "Pause" and "Menu" icons on the touch screen. If participants fail to fully open or close their hand for more than 30 seconds, the exercise stops automatically. The software also tracks and displays the number of full repetitions achieved for each exercise by assessing whether the second to fifth fingers transitioned from <20° to >50° and back to <20° range of motion (ROM) of the metacarpophalangeal joints. A performance summary is also available after each exercise. This summary included the exercise duration, total number of repetitions, and level of assistance or resistance, as well as performance outcomes from previous sessions for comparison.

Intervention: Conventional Rehabilitation Therapy and the RAHRE Program

The study aimed to demonstrate the feasibility and added value of integrating the RAHRE program into current conventional therapy (ie, pragmatic approach). In this context, the control group received only conventional therapy, and no alternative intervention was added in the context of the present feasibility study. Thus, regardless of the allocation group, all participants received conventional rehabilitation therapy (eg, massage,

passive or active ROM, sensory stimulation, strengthening exercises, and functional activities of daily living) offered by their appointed rehabilitation professionals throughout the duration of the study. Overall, each participant received approximately 7.5 hours per week of individual occupational and physical therapy [12]. Participants allocated to the experimental group (ie, RAHRE program) received an additional 30-minute session on weekdays over a 2-week period (5 sessions per week for a total of 10 sessions). Each session took place at the rehabilitation center where participants underwent their regular inpatient intensive functional rehabilitation and was supervised by a registered occupational therapist (CEP) who provided support as needed to the participant. During each session, participants engaged in the different exercises available on btrained (version 2.0).

Outcome Measures

Sociodemographic and Clinical Characteristics

Sociodemographic and clinical characteristics including age, sex, time since stroke onset, stroke type, most affected side, handedness, and technological experience were collected during the initial evaluation. With permission from MoCA Test Inc, a certified research member (CEP) administered the Montreal Cognitive Assessment (MoCA) to gather participants' cognitive scores, while the Modified Ashworth Scale (MAS) was used to assess spasticity at the elbow, wrist, fingers, and thumb of the most affected arm [13,14]. Although the study did not aim to improve these parameters, these assessments were conducted to inform the development of future inclusion and exclusion criteria for the use of the Dexmo and btrained (version 2.0) software. Additionally, the FMA-Hand score for each participant was collected to confirm eligibility as previously described.

Feasibility

The feasibility of this intervention is structured around 3 themes: recruitment, familiarization period, and intervention. For recruitment, the number of patients admitted to the rehabilitation center, the number of those identified as potentially eligible, the number of those enrolling in the study, and the number of dropouts were collected over the course of the study. For the familiarization period, the number of participants able to don the glove independently (ie, to put on the glove and wear it on their most affected hand without the need of verbal cues nor physical support from a third party) and carry out exercise level 1 was collected. For the intervention, attendance and compliance, including the session duration of the therapy session, were collected. The therapy dose and learnability, through the number of repetitions of full movement of fingers flexion and extension per session, the active training time per session, the time for the participant to independently don the glove, the level of glove assistance or resistance, and the description of any therapist verbal cueing and support necessary to help the participants navigate through btrained (version 2.0), were also collected.

Safety

At the start, during, and at the end of each session, participants were asked to inform the researcher of the presence of serious adverse effects or any discomfort believed to be associated with the training sessions and specified its intensity (mild, moderate, or high). In addition, the level of hand pain was collected using a visual analog scale (VAS) at the start and end of each session.

Function

Five functional upper extremity assessments encompassing 2 domains of the International Classification of Functioning, Disability and Health were used to measure body function and activity and participation. Body function was assessed via the primary outcome measure, the FMA-UE, as well as grip strength and lateral pinch strength. Activity and participation were assessed using the primary outcome measure, the Action Research Arm Test (ARAT), along with the Box and Block Test (BBT) and the ABILHAND questionnaire. These assessment tools are thoroughly detailed in other sources, including the Shirley Ryan AbilityLab [15] and are known to demonstrate excellent psychometric properties in stroke populations [16-19].

Satisfaction

Participants in the experimental group completed a project-specific satisfaction questionnaire at the end of the RAHRE program. The questionnaire incorporated elements of both the User Satisfaction Evaluation Questionnaire [20] and the Suitability Evaluation Questionnaire (SEQ) [21] for a total of 25 questions organized around 7 sections, each including 1 to 5 questions (see Multimedia Appendix 1 to access the full version of the questionnaire). Questions incorporated into sections 1 to 6 were scored on a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree, whereas questions incorporated in section 7 were answered on a 3-point scale depending on the item. For questions regarding duration and frequency (items 7.1-7.3), response options were: 1=adequate, 2=too short or not enough, and 3=too long or too much. For perceived effort (items 7.4-7.5), responses were: 1=mild, 2=moderate, and 3=high.

Data Analysis

All sociodemographic and clinical characteristics, feasibility, as well as participant-specific safety measures and satisfaction data are reported with descriptive statistics (ie, median and group-median %). Functional outcome measures are analyzed by comparing individual changes in scores from pre- to postintervention. Median scores for the entire group are then extracted and interpreted against established benchmarks, such as the minimal detectable change (MDC), smallest real difference (SRD), and minimal clinically important difference (MCID), when available for the specific outcome and comparable population [22]. Changes exceeding the MDC, SRD, or MCID are deemed to indicate a significant effect in that particular functional outcome and thereafter, based on the directionality of this change, judged to be beneficial or detrimental. The proportion of participants with a change exceeding the MDC, SRD, and MCID for each outcome is also reported.

Results

Feasibility

Recruitment Process

Figure 2 illustrates the recruitment process and details reasons for excluding potential participants at each step. Of 71 individuals admitted to the stroke unit of the rehabilitation center between September 15, 2023, and March 15, 2024, a total of 11 enrolled in the study, resulting in a recruitment rate of 16% and a recruitment ratio of 1.83 participants per month.

Figure 2. Recruitment flowchart.

Familiarization Period

During the familiarization period prior to initiating the intervention, most participants (8/11, 73%; except C1, C4, and E6) successfully donned the glove independently. All participants were able to complete exercise level 1. Participants were then randomized into the control (n=5) or the experimental group (n=6). Following the randomization, 1 participant from each group withdrew, resulting in a dropout rate of 18% (2/11); the participant who withdrew from the control group was discharged before the final evaluation appointment and requested data destruction, whereas the participant who withdrew from the experimental group cited being overwhelmed by learning to use technologies such as the Dexmo and btrained (version 2.0) due to age (84 years), limited technological experience, and cognitive issues (MoCA=18/30). Thus, a total of 9 participants (control group: n=4 and experimental group: n=5) completed the study. Participants' sociodemographic and clinical characteristics are provided in Table 1. Among all participants, the highest MAS score observed was 3 for elbow spasticity, while scores for wrist and finger spasticity ranged between 0 and 2.

Table . Participants' sociodemographic and clinical characteristics.

Participant	Age (year)	Sex	Stroke onset (months)	Stroke type	Affected side	Handedness	Technological experience[a]	MoCA[b] (out of 30)	FMA[c]-Hand (out of 14)
Control group									
C1	52	Male	4.1	Hemorrhagic	Right	Right	B	22	3
C3	65	Female	0.83	Ischemic	Right	Right	D	15	7
C4	30	Male	1.47	Hemorrhagic	Right	Right	C	23	5
C5	80	Male	1.19	Ischemic	Left	Right	D	20	11
Experimental group									
E1	63	Male	1.87	Hemorrhagic	Left	Right	B	27	13
E2	44	Female	1.23	Ischemic	Right	Right	B	25	9
E3	74	Female	1.13	Ischemic	Left	Right	C	24	13
E5	56	Female	0.71	Hemorrhagic	Right	Right	C	15	12
E6	22	Female	1.52	Hemorrhagic	Left	Right	A	23	1

[a]A: expert, B: competent, C: beginner, D: ignorant.

[b]MoCA: Montreal Cognitive Assessment.

[c]FMA: Fugl-Meyer Assessment.

Intervention

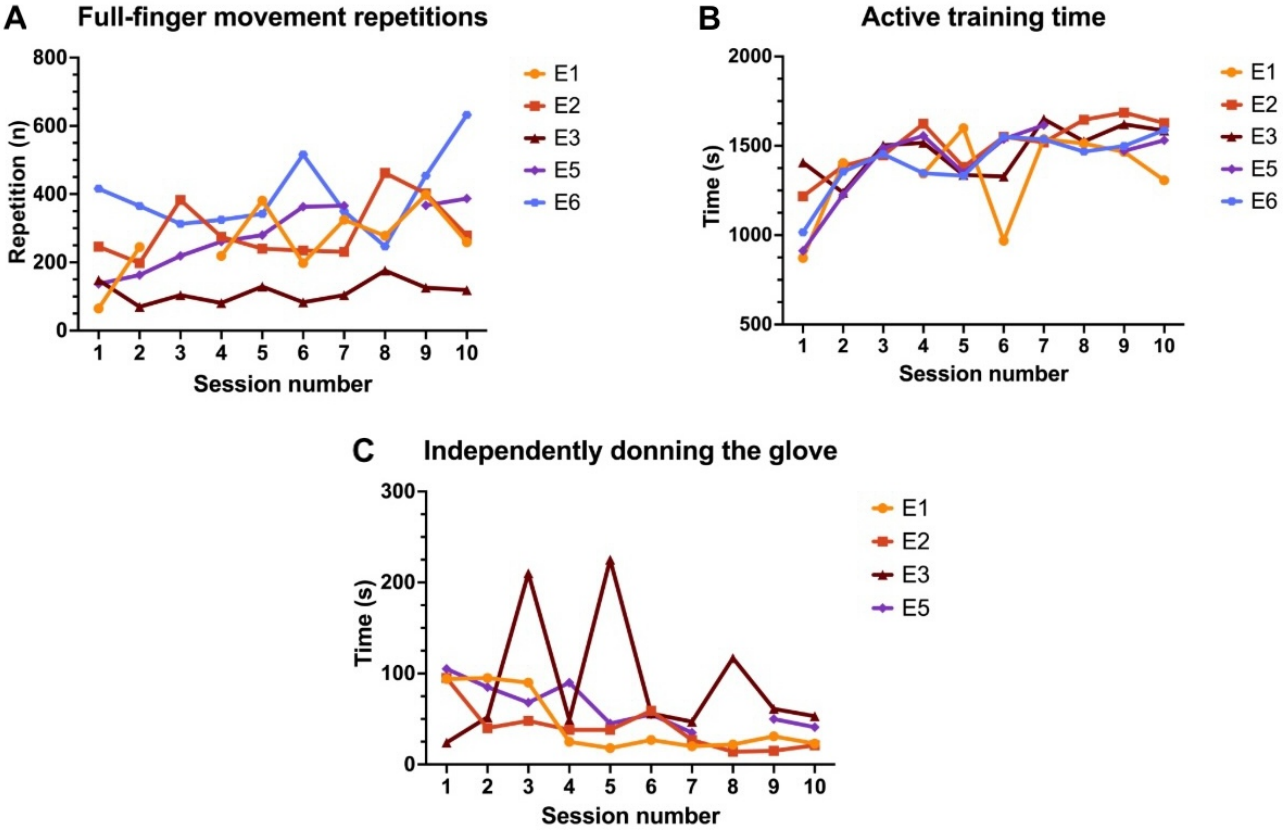
Attendance and Compliance

Most participants in the experimental group (3/5) attended all training sessions, while 2 missed 1 session each, respectively, due to a technology malfunction and a scheduling conflict. Hence, the attendance rate was 96% (48 completed training sessions of 50 planned sessions). The expected session duration was 30 minutes, including the glove donning time. Most participants (3/5) completed all 30-minute sessions as planned, though 2 sessions ended earlier than expected (ie, 19 minutes 20 seconds and 28 minutes 30 seconds) due to fatigue. The overall compliance rate was 95% (1432 completed training minutes of 1500 planned minutes).

Therapy Dose and Learnability

A summary of the number of repetitions of full-finger movement of flexion and extension, their active training time, and the time for participants to independently don the glove over the course of the study is reported in Figure 3. The number of full-movement finger flexion and extension repetitions per session ranged from 65 to 632 (median 260, IQR 173-365 repetitions), with a median active training time of 24 minutes 39 seconds (IQR 22 minutes 26 seconds-25 minutes 51 seconds). This resulted in a median intensity ratio of 10.2 (IQR 6.6-13.1) repetitions per minute of active training and 8.2 (IQR 4.4-10.5) repetitions per minute of total training session. Independent donning times ranged from 14 to 225 seconds (median 46, IQR 27-60 seconds). Only 1 participant (E6) required continuous therapist support to don the glove until the end of the program due to severe hand impairments. The median donning time for this participant with therapist support was 181 (IQR 162-195) seconds. Participants predominantly used the Dexmo glove with resistance (n=4) rather than assistance (n=1). Therapist verbal cueing and support required to navigate btrained (version 2.0) was only needed during the first 7 sessions, with a median of 6 (IQR 4-7) sessions to reach full independence. By the fifth session, 3 of 5 participants were completely autonomous. Independence was more difficult to achieve for the remaining 2 (E3 and E5), who required support, respectively, in 70% (7/10) and 40% (4/10) of sessions, while the other 3 needed assistance in no more than 20% (2/10) of sessions.

Figure 3. Participants' progression in the robotic-assisted hand rehabilitation exercise (RAHRE) program. (A) Number of full-finger movement of flexion and extension repetitions (n) completed by each participant in each session. (B) Active training time (seconds) for each participant in each session. (C) Time required (seconds) to independently don the glove for each participant capable of independent donning, for each session.



Safety

No serious adverse effect associated with the RAHRE program was reported. Most participants (4/5) experienced mild to moderate muscle fatigue in the forearm during or at the end of at least 1 session. Some participants took short breaks due to muscle fatigue during a session, and others deemed it unnecessary. Muscle fatigue never leads to a session termination. No instances of increased spasticity, hypertonicity, or other discomforts such as skin lesions, stiffness, confusion, or dizziness were observed or reported by participants during or after any of the sessions.

Hand pain was reported by 1 participant (E5) before every training session (median VAS score 2.1 per 10 cm, IQR 1.7-2.9 cm), with an increase in pain reported at the end of each session never exceeding 1 cm (median increase on VAS 0.1 per 10 cm, IQR −0.2 to 0.4 cm).

Preliminary Functional Effects

Tables 2 and 3 present the individual pre- and postintervention scores and overall change in scores for each participant, along with the group median. For each functional outcome, the tables also display the corresponding MDC or SRD, as well as the MCID, when available. Both groups demonstrated functional improvements on the ARAT, FMA-UE, and BBT, with median score changes exceeding the respective MDC or SRD values. In the control group, 50% of participants exceeded the MDC for both the ARAT and FMA-UE, and 75% exceeded the SRD for the BBT. In the experimental group, 60% of participants exceeded the MDC for the ARAT, 80% for the FMA-UE, and 60% exceeded the SRD for the BBT. For the ABILHAND, both groups also showed improvements, with median score differences exceeding the MCID. In the control group, 75% of participants exceeded the MCID. In the experimental group, 80% exceeded the MCID, while 20% showed changes below the MCID threshold in the negative direction.

Table . Individual pre- and postintervention scores, change scores, and group data scores for Action Research Arm Test (ARAT), Fugl-Meyer Assessment for the Upper Extremity (FMA-UE), and grip strength.

Group	ARAT (points out of 57) (MDC[a]=3.5 points; MCID[b]=12 - 17 points [23,24])			FMA-UE (points out of 66) (MDC=3.5 points; MCID=9 - 10 points [24,25])			Grip strength (kg) (SRD[c]=2.9 kg; MCID=5 - 6.2 kg [16,23])		
	Prescore	Postscore	Δ[d]	Prescore	Postscore	Δ	Prescore	Postscore	Δ
Control group									
Individual data									
C1	0.0	0.0	0.0	10.0	11.0	1.0	7.0	6.0	−1.0
C3	28.0	37.0	9.0	50.0	57.0	7.0	11.3	12.3	1.0
C4	1.0	10.0	9.0	17.0	26.0	9.0	0.0	4.7	4.7
C5	54.0	54.0	0.0	53.0	54.0	1.0	30.0	30.8	0.8
Group data									
Median (IQR)	14.5 (0.8-34.5)	23.5 (7.5-41.3)	4.5[e] (0.0-9.0)	33.5 (15.3-50.8)	40.0 (22.3-54.8)	4.0[e] (1.0-7.5)	9.2 (5.3-16.0)	9.2 (5.7-17.0)	0.9 (0.4-1.9)
Experimental group									
Individual data									
E1	54.0	57.0	3.0	49.0	57.0	8.0	25.0	26.0	1.0
E2	39.0	55.0	16.0	49.0	54.0	5.0	8.3	9.3	1.0
E3	55.0	57.0	2.0	57.0	59.0	2.0	12.0	16.3	4.3
E5	51.0	55.0	4.0	54.0	60.0	6.0	20.7	22.7	2.0
E6	0.0	4.0	4.0	13.0	18.0	5.0	4.0	6.7	2.7
Group data									
Median (IQR)	51.0 (39.0-54.0)	55.0 (55.0-57.0)	4.0[e] (3.0-4.0)	49.0 (49.0-54.0)	57.0 (54.0-59.0)	5.0[e] (5.0-6.0)	12.0 (8.3-20.7)	16.3 (9.3-22.7)	2.0 (1.0-2.7)

[a]MDC: minimal detectable change.

[b]MCID: minimal clinically important difference.

[c]SRD: smallest real difference.

[d]Change in score between pre- and postscores.

[e]Median score changes exceeding the respective MDC, SRD, or MCID values.

Table . Individual pre- and postintervention scores, change scores, and group data scores for lateral pinch strength, Box and Block Test (BBT), and ABILHAND.

Group	Lateral pinch strength (kg) (SRD[a]=1.4 kg [16])			BBT (blocks per minute) (SRD=5.5 blocks per minute [16])			ABILHAND (per logit) (MCID[b]=0.26 - 0.35 logits [19])		
	Prescore	Postscore	Δ[c]	Prescore	Postscore	Δ	Prescore	Postscore	Δ
Control group									
Individual data									
C1	2.2	2.2	0.0	0.0	2.0	2.0	0.0	0.3	0.3
C3	2.8	2.8	0.0	20.0	26.0	6.0	1.1	2.2	1.1
C4	0.3	1.2	0.9	0.0	7.0	7.0	−1.0	−0.4	0.7
C5	7.7	8.0	0.3	33.0	40.0	7.0	3.8	4.3	0.5
Group data									
Median (IQR)	2.5 (1.7- 4.0)	2.5 (1.9-4.1)	0.2 (0.0-0.5)	10.0 (0.0-23.3)	16.5 (5.8-29.5)	6.5[d] (5.0-7.0)	0.5 (−0.3-1.8)	1.2 (0.1-2.7)	0.6[d] (0.5-2.4)
Experimental group									
Individual data									
E1	5.8	7.0	1.3	27.0	30.0	3.0	2.6	4.3	1.7
E2	2.0	2.1	0.1	27.0	36.0	9.0	−0.8	2.0	2.8
E3	4.5	5.6	1.1	15.0	23.0	8.0	1.8	2.4	0.6
E5	4.2	6.5	2.3	35.0	42.0	7.0	−1.3	1.1	2.4
E6	0.5	0.7	0.2	0.0	2.0	2.0	0.8	0.1	−0.6
Group data									
Median (IQR)	4.2 (2.0-4.5)	5.6 (2.1-6.5)	1.1 (0.2-1.3)	27.0 (15.0-27.0)	30.0 (23.0-36.0)	7.0[d] (3.0-8.0)	0.8 (−0.8-1.8)	2.4 (1.1-2.4)	1.7[d] (0.6-2.4)

[a]SRD: smallest real difference.

[b]MCID: minimal clinically important difference.

[c]Change in score between pre- and postscores.

[d]Median score changes exceeding the respective minimal detectable change, SRD, or MCID values.

Satisfaction

Participants' median satisfaction scores for each section of the questionnaire are reported in Tables 4 and 5. Overall, participants expressed high satisfaction with the RAHRE program, Dexmo glove, and btrained (version 2.0). The program was found to be both satisfying and motivating, with participants acknowledging its high learnability and ease of use. Additionally, participants strongly agreed with the perceived health benefits associated with the RAHRE program.

Table . Satisfaction median score per section for each participant.

Domains: part 1 - 6	E1	E2	E3	E5	E6
1. Overall satisfaction with the RAHRE[a] program	5	5	5	4.5	5
2. Satisfaction with the robotic glove	5	5	5	4	5
3. Satisfaction with the virtual environment system attributes	5	5	5	4	3.5
4. Satisfaction and motivation with exercise program	5	5	4.5	5	2
5. Learning how to use the robotic glove coupled to the virtual environment system	5	4	5	5	4
6. Perceived health benefits	5	5	5	5	3

[a]RAHRE: robotic-assisted hand rehabilitation exercise.

Table . Participant's level of satisfaction with the setting of the program.

Domains: part 7: satisfaction with the setting of the RAHRE[a] program	E1	E2	E3	E5	E6
7.1. The total duration of the program, which took place over a period of 2 weeks, was	Adequate	Adequate	Adequate	Adequate	Adequate
7.2. The number of exercise sessions (5 times per week) is	Adequate	Adequate	Too much	Adequate	Adequate
7.3. The duration of each exercise session, which is approximately 30 minutes, is	Adequate	Adequate	Adequate	Adequate	Adequate
7.4. I perceived a level of physical exertion _____ during exercise sessions	Mild	Moderate	Moderate	Moderate	High
7.5. I perceived a level of cognitive effort (attention, concentration, etc) ____ during exercise sessions	Moderate	Moderate	High	High	Moderate

[a]RAHRE: robotic-assisted hand rehabilitation exercise.

Discussion

Although based on a small sample, this preliminary feasibility study suggests that adding a 30-minute high-intensity, hand-specific RAHRE program to conventional rehabilitation is feasible and safe and holds promise for improving hand function and achieving high participant satisfaction.

RAHRE Program as an Adjunct to Conventional Inpatient Rehabilitation Is Feasible

The results of this study demonstrate feasibility, first, by confirming a recruitment ratio of 1.83 participants per month, which is similar to the ratio reported in other comparable studies (ranging between 1.5 and 1.9 participants per month) [26,27]. When the project was introduced to potential participants, there were minimal refusals (n=5), indicating that the intervention was appealing and motivating for individuals with stroke. In

fact, the main reason for declining participation was their interest in enrolling in another research project, deployed simultaneously, and that aligned better with their therapeutic preferences and needs. The dropout rate of 18% exceeded the median dropout rate of 6% reported in a systematic review on recruitment in stroke rehabilitation randomized controlled trials [26]. Nonetheless, the dropout rate in this study was lower when compared to another study involving a similar number of participants and interventions, which had a dropout rate of 30% [28].

Second, the attendance rate was excellent (48 completed training sessions out of 50 planned sessions, 96%), indicating that both the frequency and duration of the novel RAHRE program (5 sessions per week; 30 minutes per session) are feasible. Such an engagement was facilitated by offering the novel program during inpatient rehabilitation, thereby reducing common attendance barriers often encountered in outpatient rehabilitation, such as transportation issues and the unavailability of caregivers to accompany participants [29]. However, applying the intervention during inpatient rehabilitation comes with other issues such as scheduling challenges due to multiple interventions and the development of fatigue as the day progresses. Future trials should carefully consider participant fatigue when scheduling the RAHRE program. Independent use of the technology, without constant therapist supervision, and ensuring its availability at all times would enable more scheduling flexibility.

RAHRE Program Can Be Performed Independently

The results of this study confirm that participants progressively achieved autonomy and independence in performing the RAHRE program. First, despite expectations of challenges in donning the Dexmo glove for individuals who have had a stroke, most participants successfully donned the glove independently, efficiently, and with ease, never exceeding the 5 - to 10-minute donning period recommended by occupational therapists to optimize therapy time [30]. In this study, the donning process typically took less than 1 minute, with or without therapist support, and there was a noticeable trend of decreased donning time across sessions, confirming improved efficiency with practice. Based on the findings, which should be interpreted with caution due to the small sample size, it is important to note that a score ≤5 on the FMA-Hand makes it challenging for individuals to don the glove independently. Conversely, as mentioned, a MAS score of ≤2 seems to be acceptable for the use of the glove.

Second, after donning the glove, the next crucial part of the intervention was for participants to become independent in navigating through btrained (version 2.0). The results confirm that within less than 1.5 weeks, all participants had achieved independence in using btrained (version 2.0). These findings are consistent with those of a similar study involving a 4-week protocol of robot-assisted poststroke rehabilitation [31], where supervised therapy gradually transitioned to unsupervised sessions after a 2-week period.

However, achieving this level of independence was markedly more challenging for 2 participants. To explain this discrepancy, participants' sociodemographic characteristics (cognition level via MoCA, age, and technological experience) were closely examined for potential determinants on the acquisition of independence in navigating through btrained (version 2.0). Initially, participants' MoCA score was considered, recognizing that a decline in cognitive functions can impact the ability to manage technology [32]. A MoCA score below 24, which is close to the known cutoff of <26 for mild cognitive impairment, may necessitate more therapist verbal cueing and support [33]. However, this criterion alone may not fully explain the phenomenon. The participant with the lowest MoCA score (15/30) did not require the most therapist verbal cueing and support. Instead, the participant who required the greatest amount of cueing and support, E3 (7/10 sessions), was the oldest at 74 years of age (9 years older than the second-oldest participant) and had no cognitive impairment. This aligns with the understanding that the recall or recognition of information encoded, a process required to navigate autonomously through btrained (version 2.0), tends to decrease with age [34]. As for experience with technologies, the 2 participants requiring the most verbal cueing and support were both technology neophytes, having solely basic knowledge of the internet. Interestingly, cognition level, age, and experience with technologies were the reasons for withdrawal given by the participant who dropped out of the experimental group. Experience with a smartphone or computer could be considered as an inclusion criterion to increase independence in navigating through btrained (version 2.0) in a future clinical study.

RAHRE Program Intensifies Hand Neurorehabilitation

The results of this study provide compelling evidence that the RAHRE program can intensify functional hand-specific movements (+260 repetitions per session for 10 days) known to be crucial to improve functional outcomes in this population. However, this intensification was inherent to the study design, where the experimental group was expected to engage in more exercise compared to the control group. Indeed, the increased exercise time for the experimental group was a direct result of the research protocol, which anticipated higher intensity of rehabilitation due to the greater amount of exercise performed. However, what is particularly noteworthy is the rapid attainment of a high level of independence by participants. The user-friendly design of the robotic glove, combined with the virtual environment, facilitated this rapid proficiency with the equipment. This design not only supports the feasibility of the RAHRE program with minimal therapist supervision but also allows participants to engage in rehabilitation activities outside conventional therapy hours and without overburdening therapists. This autonomy in exercise execution is a crucial aspect of intensifying rehabilitation, as it allows for greater flexibility and potentially enhances overall therapeutic effectiveness. The results of this study are in line with previous studies on the feasibility of unsupervised robot-assisted therapy using an actuated upper extremity device in a clinical setting that resulted in a significant increase in therapy dose [31]. Both this study and others are based on strategies aimed at enhancing practice opportunities and fostering active engagement in rehabilitation [35] by providing, beyond conventional rehabilitation hours, a novel therapy avenue for increasing therapy doses with minimal therapist supervision within clinical

settings. The high portability of the Dexmo and its virtual environment makes it possible for the RAHRE program to be extended to home-based rehabilitation.

In addition to enhancing therapy opportunities for rehabilitation, therapy dose, including the number of repetitions, resistance levels during each repetition, and the time dedicated to exercising, remains one of the key strategies to intensify hand neurorehabilitation. The median observed repetition intensity ratio of 10.2 repetitions per active training minute and 8.2 repetitions per total session minute is above what is seen in a conventional rehabilitation session. For instance, in studies focusing on the amount of repetition achieved in conventional rehabilitation sessions, the average intensity ratio was below 2.4 - 3.8 repetitions per minute [36,37], while studies focusing on high-repetition of task-specific training reported an average intensity ratio between 6.1 and 7.1 repetitions per minute [38,39]. Thus, the RAHRE program offers a higher intensity ratio than conventional therapy alone and surpasses similar studies on high-intensity training. Moreover, despite some variations, participants generally increased the number of repetitions across sessions. Lower repetition counts may have been influenced by variations in the level of glove assistance or resistance provided during exercises (eg, the higher the glove resistance, the smaller the number of repetitions). Fatigue levels toward the end of the day could also negatively influence repetitions. To optimize the functional benefits of time dedicated to exercising, the second Stroke Recovery and Rehabilitation Roundtable recommends intervention doses of more than 1 hour per day on a task [2]. While each participant received approximately 7.5 hours per week of individual conventional occupational and physiotherapy [12], not all of these hours were related to task practice. In fact, only one-third of therapy time is dedicated to task practice [40]. Therefore, supplementing conventional therapy with the 30-minute RAHRE program could help bridge this gap and align more closely with Stroke Recovery and Rehabilitation Roundtable recommendations. It remains uncertain how this intensification translates to increased effect and efficacy, and studies using a higher level of evidence (ie, randomized controlled trial) are needed.

RAHRE Program Induces Beneficial Effects

The results of this study do not provide conclusive evidence that the RAHRE program induces significant beneficial effects in terms of functional capacity, particularly for grasp-related activities. While median changes in scores for both primary outcomes, ARAT and FMA-UE, were greater than the MDC or SRD, indicating a true change, they did not exceed the MCID. This modest yet encouraging impact may be partially attributed to the brief period of the intervention (eg, duration), combined with its early implementation in the poststroke period, a phase during which spontaneous recovery is frequently observed [41]. Given the neuroplastic changes and endogenous repair mechanisms active during this acute phase, the functional improvements observed in both groups likely reflect, at least in part, natural recovery processes rather than the effects of the intervention alone. To more accurately isolate and assess intervention-specific effects, longer intervention periods, typically exceeding 5 weeks, are generally more effective in eliciting measurable gains in fine motor control.

Moreover, the small sample size of our study limited the ability to perform comparative analyses, such as *t* tests, and to detect any potential superior effects of the RAHRE program over conventional therapy alone. Nevertheless, previous meta-analyses have confirmed that rehabilitation with robotic gloves results in significant functional improvements compared to conventional rehabilitation alone [6]. Future efficacy studies with larger sample sizes are needed to assess the potential superiority of the RAHRE program compared to conventional therapy. Based on a power analysis using G*Power (version 3.1.9.4; Heinrich Heine University Düsseldorf) software, such studies should aim for a sample size of 106 participants (53 per group) to achieve a statistical power of 0.8 with a 2-tailed *t* test at a significance level of .05. This calculation accounts for a medium-large effect size (Cohen d=0.6), normal distribution of outcomes, and an 18% dropout rate observed in this study. In these future studies, the control group should receive an alternative hand-targeted exercise therapy of equal duration and intensity as the experimental group, but without the glove and virtual reality. This would allow for a more accurate assessment of the superiority of the RAHRE program compared to nontechnological alternatives.

The selection of outcome measures to capture changes both in gross and fine hand sensorimotor recovery and their impacts on functional activities was a challenge in this study. Typically, gross motor movements are inherently easier to perform compared to tasks requiring fine dexterity [42]. Given that the RAHRE program led to beneficial changes in both overall upper extremity outcomes (FMA-UE and ARAT) and gross dexterity outcome (BBT), it would be relevant to further explore the effect of the RAHRE program on fine dexterity. To do so, incorporating the Nine-Hole Peg Test as an additional outcome would be effective to measure functional progress in terms of fine dexterity, especially for individuals with less severe impairments [43].

RAHRE Program Is Safe and Satisfying

The results of this study support that the RAHRE program is clinically safe and satisfying for participants. While it is not uncommon for studies involving virtual reality to report instances of dizziness, soreness, headaches, nausea, or visual disturbance [44], none were observed in this study. In fact, no serious adverse effect was documented. Participants only reported mild to moderate muscular fatigue and physical exertion aligning with the American Heart Association and American Stroke Association for exercise intensity recommendations to prevent subsequent stroke and other cardiovascular events [45]. As for the presence of moderate to high cognitive effort, the results are consistent with studies showing positive effects of motor-cognitive interventions on physical and cognitive functioning [46,47]. These findings, along with the high level of satisfaction, are similar in most part to those of Warland et al [48], who observed unaccustomed muscular pain, cognitive fatigue, perceived improvements in impairments and functional use, and a high level of motivation among participants using a virtual reality–based upper-extremity stroke rehabilitation device. Nonetheless, before the RAHRE program is adopted as a routine intervention in clinical practice, it would be relevant to evaluate its safety in a broader

framework, including adherence to standard protocols for safety evaluation, testing, and risk management for medical devices.

Limitations

Some limitations should be acknowledged to contextualize the results of this feasibility study. First, the small sample size and the considerable variability in participant characteristics (eg, age, sex, stroke type, and affected side) and baseline scores within each group need to be highlighted. It did limit the statistical power to detect between-group differences and identify statistically or clinically meaningful changes attributable to the intervention. However, it is crucial to emphasize that the primary aim of this feasibility study was to assess the practical implementation of the intervention rather than to establish its efficacy. As such, while the study provides insights into feasibility, it underscores the need for future research with larger sample sizes and more rigorous research designs to strengthen evidence regarding the efficacy of the RAHRE program. A larger sample size would also enable subgroup analyses based on various sociodemographic and clinical factors (eg, age, sex, stroke type, most affected side, and FMA-Hand score), providing a more nuanced understanding of how these variables may influence outcomes. Second, the high level of satisfaction toward the program may reflect a desirability bias, as the same person (CEP) both supervised the intervention and collected satisfaction data. To mitigate this bias in future studies, an independent evaluator should conduct the satisfaction assessments. Third, blinding to randomization was maintained only during the initial evaluation, as the occupational therapist (CEP) was also administering the intervention. Participant blinding was not feasible due to the intervention's nature. Fourth, the number of repetitions performed may have been underestimated. In fact, the number of movement repetition compatibilized in btrained (version 2.0) only accounted for full flexion and extension movements. Similarly, for exercises 3 and 4, only repetitions performed in sync with the metronome were counted, excluding any full flexion and extension movements that deviated from the tempo provided. Finally, achieving ROM targets in extension poses challenges compared to flexion due to longer-lever arms when participants' fingers were in an extension motion. To better accommodate these biomechanical differences, adjusting glove resistance torque levels independently for flexion and extension would be crucial in future iterations of the RAHRE program.

Conclusions

The RAHRE program emerges as a feasible intervention from a clinical perspective that demonstrates encouraging beneficial effects for hand functional recovery. Moreover, the intervention remains safe and satisfying for people who sustained a stroke currently undergoing inpatient intensive functional rehabilitation (ie, end users). This innovative program, which combines the Dexmo glove and the btrained (version 2.0) platform, offers an avenue to intensify hand rehabilitation. Notably, the RAHRE program can be used independently by individuals with stroke with minimal support from a rehabilitation professional. Undertaking an efficacy study on a broader scale and for an extended duration would greatly enhance the strength of currently available evidence and inform practical applications of this novel intervention in the future.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CEP led the conceptualization of the study, with equal contributions from DHG and JH. Data curation, formal analysis, investigation, and visualization were primarily conducted by CEP. Methodology development was led by CEP, with equal support from DHG and JH. Project administration was also led by CEP, with equal support from DHG and JH. Resources were provided equally by DHG, JH, TV, and MH. Software development was equally supported by TV and MH. Supervision was led by DHG, with support from JH. CEP led the writing of the original draft. All authors contributed to the review and editing of the manuscript, with CEP leading this process; DHG and JH contributed equally, and TV and MH provided supporting input.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Project-specific satisfaction questionnaire.
[DOCX File, 27 KB - neuro_v4i1e69750_app1.docx]

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Abbreviations

ARAT: Action Research Arm Test
BBT: Box and Block Test
FMA-UE: Fugl-Meyer Assessment for the Upper Extremity
MAS: Modified Ashworth Scale
MCID: minimal clinically important difference
MDC: minimal detectable change
MoCA: Montreal Cognitive Assessment
RAHRE: robotic-assisted hand rehabilitation exercise
ROM: range of motion
SRD: smallest real difference
VAS: visual analog scale

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Exploring Remote Monitoring of Poststroke Mood With Digital Sensors by Assessment of Depression Phenotypes and Accelerometer Data in UK Biobank: Cross-Sectional Analysis

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Abstract

Background: Interest in using digital sensors to monitor patients with prior stroke for depression, a risk factor for poor outcomes, has grown rapidly; however, little is known about behavioral phenotypes related to future mood symptoms and if patients with and without previously diagnosed depression experience similar phenotypes.

Objective: This study aimed to assess the feasibility of using digital sensors to monitor mood in patients with prior stroke with a prestroke depression diagnosis (DD) and controls. We examined relationships between physical activity behaviors and self-reported depression frequency.

Methods: In the UK Biobank wearable accelerometer cohort, we retrospectively identified patients who had previously suffered a stroke (N=1603) and conducted cross-sectional analyses with those who completed a subsequent depression survey follow-up. Sensitivity analyses assessed a general population cohort excluding previous stroke participants and 2 incident cohorts: incident stroke (IS) and incident cerebrovascular disease (IC).

Results: In controls, the odds of being in a higher depressed mood frequency category decreased by 23% for each minute spent in moderate - to - vigorous physical activity (odds ratio 0.77, 95% CI 0.69 - 0.87; *P*<.001). This association persisted in both general cohorts and in the IC control cohort.

Conclusions: Although moderate - to - vigorous physical activity was linked with less frequent depressed mood in patients with prior stroke without DD, this finding did not persist in DDs. Thus, accelerometer-mood monitoring may provide clinically useful insights about future mood in patients with prior stroke without DDs. Considering the finding in the IC cohort and the lack of findings in the IS cohorts, accelerometer-mood monitoring may also be appropriately applied to observing broader cerebrovascular disease pathogenesis.

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KEYWORDS

depression; cerebrovascular disease; remote monitoring; stroke; accelerometers; mobile phone

Introduction

Overview

Depression is an established risk factor for poor outcomes after a stroke and transient ischemic attack (TIA), including subsequent stroke and other cerebrovascular diseases (CeVDs) [1,2]. Although poststroke depression (PSD) affects roughly one-third of patients with stroke, screening for depression in patients after a stroke is not routine, with less than 10% of patients with stroke screened [3]. Furthermore, it remains unclear when follow-up PSD screening should occur, as current research suggests that not all patients will experience PSD symptoms immediately after a stroke and, for those who do, the majority will experience recurrent depression episodes in the years after a stroke [4]. A reason for this gap in screening is the shortage of neurologists, particularly those with diagnostic training in identifying PSD [5]. Accelerated by the widespread adoption of personal mobile devices, from computers to smartwatches, it is critical to investigate the potential of such devices to collect meaningful data outside of clinical settings, aiding clinicians in identifying depressed mood in patients with

stroke—and, potentially, those most at risk for subsequent stroke and CeVDs [6].

Background

The prevalence of PSD remains unknown, partly due to its heterogeneous nature, spanning unique somatic, behavioral, cognitive, motivational, and emotional components [7]. The severity of its manifestation ranges from mild symptoms to clinical-grade depression, the former of which relies on self-reported scoring methods inherently subject to bias, especially in patients with cognitive impairment for whom self-reported surveys may not be reliable [8]. Although clinician-administered assessments, like the Montgomery–Åsberg Depression Rating Survey (MADRS), offer gold-standard assessments of symptoms, nurse and physician shortages complicate the routine administration of such instruments [9].

In some survivors, depression may emerge alongside the incipient pathogenesis of cerebrovascular dysfunction, while for others, depression may be a reaction to being conscious of cognitive impairment or the putative manifestation of silent cerebral infarcts [10,11]. As such, individual depression phenotypes may vary greatly across survivors with identical survey summary scores. Although investigations into the associations between stroke location within the brain and self-reported depression survey scores have yielded inconclusive results, a recent cross-sectional study of patients with prior stroke (n=200) found that symptoms assessed by MADRS correlate with specific macrostructural characteristics [12]. Considering that clinician-administered assessments, like MADRS, are more accurate than self-reported survey scores in patients with prior stroke, the need for a modified approach to monitoring patients with stroke for depression emerges.

In recent years, objective data from portable and wearable sensors have demonstrated the feasibility of augmenting self-reported mood surveys outside of clinics, a promising approach for monitoring patients with symptomatic and asymptomatic deteriorating brain health outside of standardized, clinical environments [13-20]. In addition, accelerometer measures of behavior have established a difference in PA engagement stratified by depression severity, highlighting the need for a thoughtful approach to PSD screening and monitoring that ensures patients with emerging or mild depression symptoms, unlike those with previous documented depressive episodes, are not neglected [21].

While triaging patients with PSD for preventative intervention could yield clinically meaningful functional recovery outcomes, the potential of such an approach for preventing future CeVD diagnoses remains to be seen. Numerous studies have found that depressive symptoms are associated with an increased risk of subsequent CeVD, from acute CeVDs, like stroke and TIA, to more chronic conditions, like cerebral arterial stenosis and vascular dementia [11,22-24]. Furthermore, recent research suggests daily functioning and cognitive changes may be observable up to 10 years before some types of CeVD [25]. Thus, particular attention should be paid to behavioral patterns in patients with PSD to elucidate phenotypes with predictive potential for functional outcomes and neurologic disorders.

Previous Work

Blending self-reported assessments of phenomena, like mood, recorded through web browsers and smartphone apps, with passive sensor data, like that from wearable accelerometers, is gaining popularity in real-world settings [26,27]. Numerous pilot studies have demonstrated the potential for wearable and minimally invasive sensors to detect neurologic conditions; however, these tools have neither been validated in population cohorts nor combined with survey sampling of mood [28].

Early-stage evidence suggests that monitoring lifestyle behavior and mood in PSD is feasible [29-31]. The results of a small longitudinal study (n=40) suggest that self-reported moderate-to-vigorous physical activity (MVPA) before stroke is associated with improved mobility and self-care as well as decreased discomfort after stroke [32]. While the study did not sample mood outside of clinical environments, Reinholdsson et al [33] used self-report surveys to expand on the above findings, demonstrating that patients who engage in higher levels of prestroke physical activity (PA) experienced less severe PSD compared with patients who were physically inactive .

In addition, current literature on accelerometers in PSD suggests that distinct behavioral patterns may identify patients with depression within the first year after a stroke. In a 2022 prospective observational study of recently discharged patients with minor ischemic stroke (n=76), participants wore accelerometers in-hospital for 1 week. Analyses revealed that only increased sedentary behavior (SB) and reduced light physical activity (LPA) were linked with more intense depression, assessed through a written Geriatric Depression Scale survey, 3 months after hospitalization in this older adult cohort [34]. In a small pilot study (n=40) of stroke survivors, MVPA was linked with positive mood [35]. Although extensive research has confirmed links between sleep disorders and both depression and incident CeVD (IC), no research has observed both depressive symptoms and objectively measured sleep after stroke [36,37]. Furthermore, no previous accelerometer research into PSD beyond the first year of stroke recovery has been published.

Goal of This Study

The goal of this study is twofold: first, to investigate potential associations between objectively measured behavior and future depression frequency in patients with prior stroke assessed by a remote approach and second, to explore whether that association varies between patients with prior stroke with a prestroke depression diagnosis (DDs) and those without (controls).

We conducted a cross-sectional analysis with the UK Biobank (UKBB), the most extensive lifestyle and mood cohort to date, assessing the relationships between accelerometer-measured sleep, SB, LPA, and MVPA and a subsequent depression descriptor (depressed mood frequency). Given that depression before stroke may yield behavioral phenotypes distinct from those emergent in participants without a prestroke depression diagnosis, we created 2 cohorts of patients with prior stroke: those with a clinical depression diagnosis before stroke and those without. As this analysis focuses on participants who may

develop or have undiagnosed PSD, participants whose PSD diagnosis was recorded were excluded. Adjusting for age, sex, ethnicity, multiple relevant comorbidities, and time elapsed between accelerometer monitoring and depression survey submission, we hypothesized that increased LPA and MVPA time would be associated with a reduction in the odds of being in a more frequent depressed mood category while increased SB time would be associated with a rise in the odds of being in a more frequent depressed mood category. Considering the established relationship between sleep and depressed mood, we created a binary variable (yes or no) for guideline-recommended sleep (7 - 9 h/d). We hypothesized that guideline-recommended sleep would be associated with a reduction in the odds of being in a more frequent depressed mood category.

Methods

Recruitment

The UKBB enrolled middle-aged (40 - 69 y) participants (N=502,364) at 22 assessment centers across the United Kingdom at a baseline assessment (2006 - 2010), which included in-person interviews, touchscreen surveys, and physical examinations to extract lifestyle and environmental data used in this study. Although all baseline participants (n=502,151) were invited, only 72,652 enrolled in the 1-week accelerometer study (2013 - 2015) and completed the depression frequency survey (2016 - 2017). Hospital and other diagnostic registries were linked to enrolled participants.

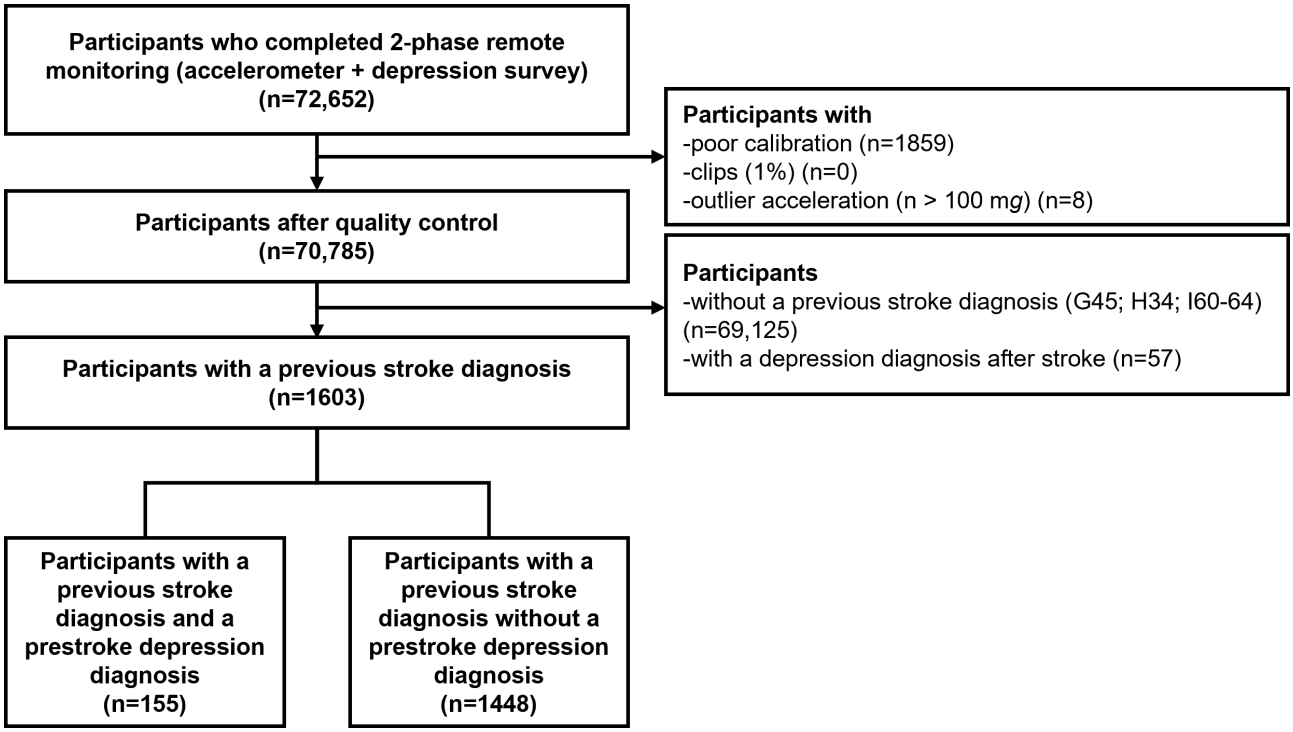
Participant Cohorts

Among participants who completed both remote monitoring components, those with dementia (n=23) were excluded. Quality control filtering demonstrated by Madjedi et al [38] was applied (n=70,785), which excluded those with outlier acceleration (>100 mg), more than 1% of readings exceeding ±8 *g* (clips), accelerometer wear time less than 3 days, and missing data for at least one 60-minute interval throughout 24-hour periods. Only participants with a previous stroke, including ischemic stroke, hemorrhagic stroke, and TIA (G45), were included (n=1660). Retinal artery occlusion (H34) was included as a stroke, as it is now considered a type of acute ischemic stroke [39]. Participants who were diagnosed with depression after stroke but before the accelerometer study (n=57) were excluded.

Among those meeting the inclusion criteria (n=1603), participants were divided into two cohorts: (1) those with a prestroke depression diagnosis at accelerometer study commencement (n=155) and (2) controls, that is, those without a prestroke depression diagnosis (n=1448) (Figure 1). No participants were diagnosed with depression between the accelerometer study and the follow-up depression survey.

Participants with a history of depression (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes F32-39) comprised the depression diagnosis (DDs) cohort. Definitions (*ICD-10* codes) used for inclusion and exclusion criteria as well as diagnostic classification are available in Multimedia Appendix 1.

Figure 1. Classification algorithm for participant cohorts.



Data Collection

Accelerometer study participants were instructed to wear the Axivity AX3 commercial accelerometer wristwatch continuously on their dominant arm for 1 week. The depressed mood frequency question was administered through a link accessible on smartphone, tablet or PC browsers as part of the standardized Patient Health Questionnaire-2 (PHQ-2) survey: “Over the past two weeks, how often have you felt down, depressed, or hopeless?” Responses were ordinal scores indicating the

frequency of depressed mood, with 1="Not at all"; 2="Several days"; 3="More than half of days"; and 4="Nearly every day."

Permanent covariables were obtained at baseline visit, including sex and ethnicity. For each participant, age at the time of accelerometer study was calculated. Time-to-assessment was individually calculated by subtracting the accelerometer start date from the date of submitting the depressed mood survey. Comorbidity diagnoses before the accelerometer study were obtained from linked patient and hospital databases.

Statistical Analysis

To compare continuous and categorical covariables, the Mann-Whitney U test and χ^2 test, respectively, were used. A cross-sectional analysis using ordinal logistic regression to investigate the association between objective behavior predictors and the ordinal outcome variable, depressed mood frequency over the past 2 weeks, was conducted on data obtained at the accelerometer study and remote follow-up survey.

For both DD and control cohorts, separate models were fitted to evaluate whether the role of objective behavior predictors in depressed mood frequency differed between cohorts.

Analyses were performed in R (R Foundation for Statistical Computing), using *polr* from the library MASS. The effect sizes of objective behavior predictors, adjusted for confounders, on depressed mood frequency were plotted as odds ratios with 95% CIs. The Likelihood Ratio Test was used to obtain all *P* values and associated CIs. $P<.05$ was statistically significant.

Sensitivity Analysis

Three sensitivity analyses (also using ordinal logistic regression models), each considering DDs and controls, were performed using UKBB data. First, a general population dataset wasf generated. This included all participants eligible for inclusion in the accelerometer study and follow-up depression frequency survey who did not have a previous stroke diagnosis.

Next, participants with an initial IC diagnosis (after the depression frequency survey) were filtered into a separate dataset. Ordinal logistic regression models were fitted to assess the relationships between objective behavior predictors and depressed mood frequency. Finally, participants in the IC cohort who had an IS diagnosis were filtered into a separate dataset, and ordinal logistic regression models were fitted to assess the target relationship. The investigation of IC as a composite end point reflects updated understanding of stroke as sharing etiology with other neurologic rather than circulatory system disorders, as defined in the most recent *International Classification of Diseases, Eleventh Revision* (*ICD-11*) [37].

For each filtered cohort, sample characteristics were obtained for review.

Ethical Considerations

National Health Service Research Ethics Committee (11/NW/0382) granted ethical approval for the UKBB population cohort study. Informed consent was obtained from all UK Biobank participants under National Health Service National Research Ethics Service (Ref 11/NW/0382). All UKBB data are deidentified.

Results

Study Characteristics

For participants in the 2-stage remote monitoring study (Table 1), the DDs had a higher proportion of women compared with controls (58.7% vs 40.7%). On average, DDs were younger (64 vs 66 y), slept slightly longer (9.2 vs 9.0 h/d), spent slightly less time in MVPA (29.3 vs 37.3 min/d) and SB (580.1 vs 583.6 min/d), and spent slightly more time in LPA (281.4 vs 278.2 min/d).

Table . Baseline characteristics of patients with previous stroke.

		Prestroke depression	Controls	*P* value
Number of participants, n		155	1448	
Age, mean (SD)		64 (7)	66 (6.5)	<.001
Gender, n (%)				
	Men	64 (41.3)	859 (59.3)	<.001
Race, n (%)				
	White	153 (98.7)	1418 (97.9)	.68
Sleep, mean (SD)		9.2 (1.8)	9.0 (1.8)	<.001
Sleep (7 - 9 h/d), n (%)		71 (45.8)	736 (50.8)	.27
SB[a], mean (SD)		580.1 (114.4)	583.6 (112.8)	<.001
LPA[b], mean (SD)		281.4 (106.9)	278.2 (102.4)	<.001
MVPA[c], mean (SD)		29.3 (31.2)	37.3 (33.0)	<.001
Time-to-assessment, mean (SD)		1.8 (0.7)	1.8 (0.6)	<.001
Diabetes, n (%)		21 (13.5)	130 (9.0)	.09
Hyperlipidemia, n (%)		76 (49)	615 (42.5)	.14
Hypertension, n (%)		155 (100)	1448 (100)	1
Multiple strokes, n (%)		40 (25.8)	348 (24.0)	.70
Time since most recent stroke, mean (SD)		7.8 (6.4)	9.8 (8.8)	<.001

[a]SB: sedentary behavior.

[b]LPA: light physical activity.

[c]MVPA: moderate-to-vigorous physical activity.

All participants had a hypertension diagnosis. The average time between accelerometer study start and depressed mood survey submission (time-to-assessment) was 1.8 years for both cohorts.

The average time from the initial stroke to the accelerometer study commencement was less for DDs than controls (7.8 vs 9.8 y).

Among DDs, 9 participants slept less than 7 hours while 75 slept more than 9 hours. In the control group, 79 participants slept less than 7 hours while 633 slept more than 9 hours.

Cross-Sectional Analysis

No significant association persisted in both the DD and control cohorts (Table 2). In controls, for each minute spent in MVPA per day, the odds of being in a higher depressed mood frequency category decreased by 23% (*P*<.001).

Table . Ordinal logistic regression assessing objective behavior predictors and depressed mood frequency.

Previous stroke participants	Prestroke depression		Controls	
	OR[a] (95% CI)	*P* value	OR (95% CI)	*P* value
Sleep (7 - 9 hr/d)	0.49 (0.23 - 1.03)	.06	0.88 (0.66 - 1.19)	.41
SB[b] (min/d)	1.00 (1.00 - 1.01)	.10	1.00 (1.00 - 1.00)	.63
LPA[c] (min/d)	1.00 (0.99 - 1.00)	.20	1.00 (1.00 - 1.00)	.35
MVPA[d] (min/d)	0.86 (0.64 - 1.17)	.33	0.77 (0.69 - 0.87)	<.001

[a]OR: odds ratio.

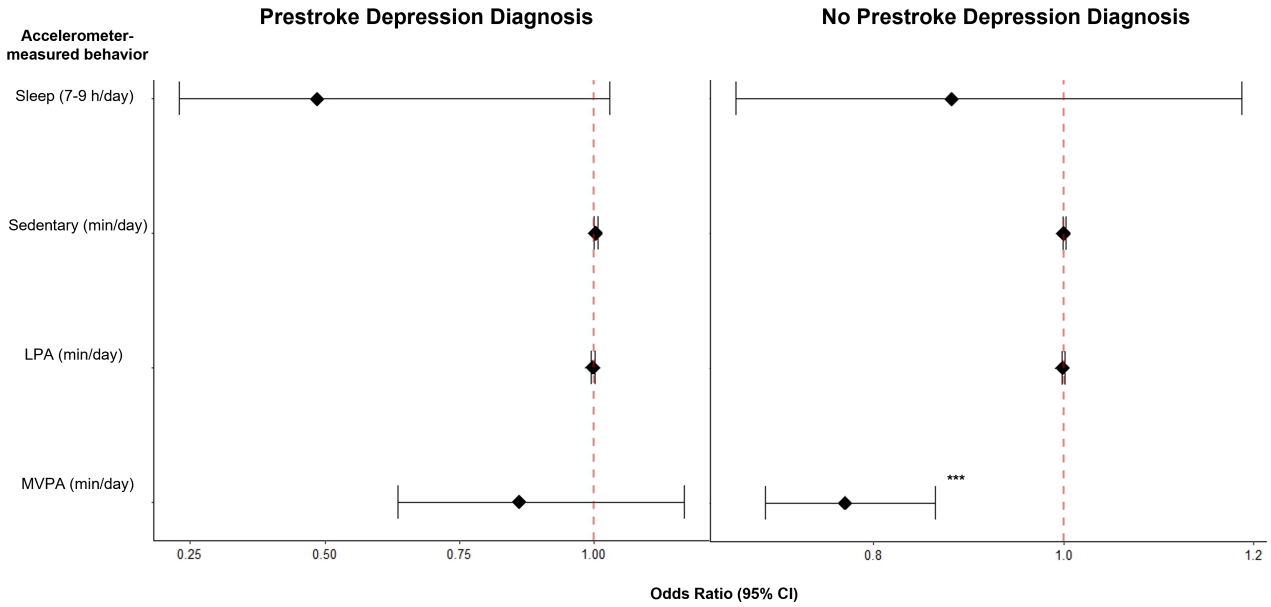
[b]SB: sedentary behavior.

[c]LPA: light physical activity.

[d]MVPA: moderate-to-vigorous physical activity.

Models were adjusted for age, sex, ethnicity, time-to-assessment, hyperlipidemia diagnosis, and diabetes diagnosis. Odds ratios (ORs) with 95% CIs for frequency of depressed mood are reported (Figure 2). ORs above 1 correspond to an increase in the accelerometer-measured behavior associated with increased depressed mood frequency.

Figure 2. Forest plot of odds ratios for depressed mood frequency by accelerometer-measured behavior comparing participants with prestroke depression diagnosis (DDs) and control cohorts. LPA: light physical activity; MVPA: moderate-to-vigorous physical activity. *** denotes statistical significance.



Sensitivity Analysis

Study Characteristics

In each filtered cohort (Multimedia Appendix 2), DDs were younger than controls (general cohort: 60 vs 62 y; IS: 64 vs 66 y; IC: 65 vs 67 y) and had a greater proportion of females (69.4% vs 56.8%; 60.0% vs 45.6%; 61.8% vs 45.1%). In the general population cohort, DDs had a greater proportion of White participants (97.7% vs 97%). On average, DDs also spent less time across cohorts in MVPA (35.0 vs 42.9 min/d; 31.0 vs 39.5 min/d; 32.0 vs 38.4 min/d), less time in LPA (295.0 vs 300.3 min/d; 286.7 vs 291.0 min/d; 287.5 vs 287.7 min/d), and more time asleep (9.1 vs 8.9 h/d; 9.1 vs 9.0 h/d; 9.04 vs 8.98 h/d).

While DDs in the general cohort spent slightly less time, on average, in SB than controls (564.3 vs 564.4 min/d), DDs in the IS and IC cohorts spent more time sedentary on average (577.1 vs 569.9 min/d; 578.2 vs 575.3 min/d).

In the general cohort, DDs had a higher proportion of diabetes (4.4% vs 2.9%) and hyperlipidemia (17.9% vs 14.9%) diagnoses and a lower proportion of participants with optimal sleep duration per day (49.5% vs 55.4%).

For the IS cohort, the average time from the completion of the depression survey to first stroke diagnosis was slightly more for DDs (1.9, SD 0.7 y) than controls (1.8, SD 0.6 y). In the IC cohort, the average time from the completion of the depression survey to first CeVD diagnosis was similarly more for DDs (1.9, SD 0.7 y) than controls (1.8, SD 0.7 y).

Cross-Sectional Analysis

In the general model (Multimedia Appendix 3), for each minute spent in MVPA, the odds of being in a higher depressed mood frequency category decreased by 18.4% (P<.001) and 13.5% (P<.001) for DDs (n=6096) and controls (n=62,589), respectively.

Also in the general model, specific only to controls, getting guideline-recommended sleep hours (7 - 9 h) each day was associated with a decreased odds of being in a higher depressed mood frequency category (5.3%; P=.02).

No significant associations were identified for those in the IS-only cohort (Multimedia Appendix 4).

For the final sensitivity analysis (Multimedia Appendix 5), assessing only those participants with an IC diagnosis, including stroke, the odds of being in a higher depressed mood frequency category decreased by 12.2% for each minute increase in MVPA (P=.03), only in controls (n=1526).

Discussion

Principal Findings

This investigation partially supports the hypothesis that objective behavior predictors would be associated with future depressed mood frequency. Although we found no significant associations between depressed mood frequency and SB, LPA or sleep for patients with prior stroke, regardless of prestroke depression diagnosis, we did find that the odds of being in a higher depressed mood frequency category decreased for each minute spent in MVPA; however, this association was only observed in participants without a prestroke depression diagnosis. This finding supports the exploratory aim of this manuscript, suggesting that participants with prestroke depression may experience different behavioral patterns compared to those without a prestroke depression diagnosis. Such a finding can potentially help clinicians tailor programs monitoring patients at risk of PSD.

The sensitivity analysis in the general cohort corroborates established findings that MVPA confers a protective effect on

mood, regardless of previous depression diagnosis. The lack of findings for the sensitivity analysis including only IS cases may be driven by the small sample sizes; however, the lack of findings also brings into question the potential for accelerometers to capture clinically actionable aberrations in patients before a stroke. Given that the protective effect of MVPA on depressed mood frequency was observed in the control cohort of patients with IC, accelerometer monitoring may be more appropriately directed to assess a broader range of neurologic changes, not just those linked with strokes.

Overall, the results suggest that accelerometer-based monitoring of behavior linked to depressed mood frequency may help clinicians identify patients who would benefit from resource-intensive screening, like the MADRS assessment. The sensitivity analyses support a separate approach for monitoring patients with a previous depression diagnosis, or more severe depression, compared to those with no documented depression or mild undiagnosed depression. When applied to predictive monitoring, a remote accelerometer-mood survey approach may be useful in cohorts of patients without a previous depression diagnosis, considering that patients with IC without clinical depression may experience observable behavior and mood changes before a CeVD diagnosis while their clinically depressed counterparts may not.

Limitations

A chief limitation of this study is that self-report data, like the depressed mood frequency survey, are subject to inaccuracies. Self-reported bias in survey responses may lead to misclassification of depressive symptom frequency and could influence different time-dependent results in our cohorts. Furthermore, the frequency of depression measures was not obtained by a clinician-graded protocol but, rather, by a survey questionnaire. Also, as the accelerometer study was only administered for one week and, on average, over a year before the follow-up mood survey, the impact of time between the objective measures and follow-up could have introduced substantial changes. The lack of associations observed for DDs may be due to the small sample size of participants with a previous depression diagnosis across cohorts. Moreover, the accelerometer study was only 1-week long and, therefore, may not generalize well to accurately represent busier or less busy weeks for patients. Accelerometer data collected on weekends versus weekdays may be distinct; however, this was not considered in this study.

The dichotomous investigation of clinically depressed and control patients are study strengths. In addition, UKBB participants were primarily White, limiting the generalizability of our findings outside of European populations. This UKBB study also primarily included participants aged 60 years and older and, as such, may not generalize well to young or middle-age adult populations. The majority of DDs were female across cohorts, a frequent finding in studies; however, male patients are less likely to seek out mental health resources, and the cohort stratification may be impacted by this.

Also, in the main analysis of previous stroke patients, participants diagnosed with clinical-grade depression after first stroke were excluded from this analysis. Considering the long gap in time from initial stroke to accelerometer study commencement, participants with a more immediate PSD diagnosis may either exhibit more intense symptoms or experience an underlying pathogenesis distinct from participants whose PSD symptoms are mild or emerge in the years after stroke.

Combining stroke types together as a single end point, as was done in the main analysis as well as the IS sensitivity analysis, may not consider unique characteristics of each stroke type and, as such, generated no significant results. Sleep was also assessed as a daily composite value, without consideration for time spent in a nap or broken sleep throughout the day. Together, these 2 limitations may have introduced confounding effects when considering sleep and depressed mood frequency, as previous research has shown short and long sleep to be associated with increased risk of intracerebral hemorrhage and ischemic stroke, respectively [40]. Furthermore, considering that all participants in our cohorts were hypertensive, MVPA's protective effect on depressive mood frequency may occur through improved cardiovascular health, rather than by conferring direct cerebral effects.

Comparison With Previous Work

No previous study assessed objective behavior measures and self-reported depressed mood frequency in patients with prior stroke years after their initial diagnosis. A key problem inherent in accelerometer research is that adherence to study designs is less-than-satisfactory for most studies [41]. This study also excluded participants with a more immediate PSD diagnosis, considering only those with prestroke depression diagnoses or those with no or mild depression after stroke. A self-report survey study of recent patients with prior stroke found that patients with high levels of PA before a stroke experienced less severe PSD [33]. Although our study could not confirm this analysis due to the design of the UKBB study, we extended those results by confirming that MVPA confers a protective effect on mood before a CeVD diagnosis in patients without a previous depression diagnosis, but not before a stroke-only diagnosis.

One plausible explanation for the lack of association between MVPA and depressed mood frequency in DDs may be that stroke survivors with a previous depression diagnosis have persistently deficient levels of brain-derived neurotropic factor (BDNF), a trophic factor released after exercise that is linked with improved mood benefits. It is well established that stroke patients in general have lower levels of BDNF, a marker of poor functional recovery [42]. The lack of a link between improved mood and MVPA in DDs may be driven by a less intense "exercise high" due to reduced or impaired BDNF function. In addition, other contributing factors, such as time spent in MVPA or neuroinflammation, may play a role in modulating BDNF expression in DDs. Of note, the lack of a significant association between MVPA and depressed mood frequency in participants with a previous depression diagnosis may be attributed to less time spent in MVPA compared with controls across all cohorts (patients with prior stroke, general population, IS, and IC). Time spent in MVPA may need to exceed a time threshold in

participants with previous depression diagnoses to improve mood.

The significant findings for IC cases, compared with the lack of findings for IS-only cases, are consistent with the updated *ICD-11* classification of CeVDs as a type of brain disease with shared etiology, rather than circulatory system disorders [37]. The protective effect of guideline-recommendation sleep (7 - 9 h/d) only observable in controls in the general cohort corroborates established work; however, the lack of associations across other cohorts may be explained by high levels of individual variability in sleep patterns, that is, nighttime disturbances, insomnia, and so on, previously identified in patients with depression as well as those at high risk of stroke [43,44].

A small pilot study of patients with minor ischemic stroke that found SB was positively associated with depression intensity and LPA was inversely associated with depression intensity [34]. Considering that this accelerometer study was conducted within the first 3 months after hospital discharge, our results extend these findings to look at mood in the years after a stroke. For instance, SB and LPA may be significant to monitor in the months after a stroke, while MVPA may be appropriate to monitor in the years after a stroke. Alternatively, MVPA may be less useful to monitor in minor ischemic stroke cases.

Using a larger dataset, our study builds on the feasibility demonstration of a small real-world study with patients with prior stroke, years after diagnosis, collecting one week of accelerometer data and ecological momentary assessments [45]. The results of our general cohort analysis considering participants without a previous depression diagnosis align with those from Sarris et al [46], who found that self-reported optimal sleep and PA were linked with decreased frequency of depressed mood in UKBB participants.

Conclusions

Our results highlight the importance of encouraging MVPA in patients with prior stroke without a depression diagnosis. Patients with prior strokes may be able to minimize short- and long-term disability and improve outcomes by proactively managing depressive symptoms. Applying MVPA to improve mood provides the added benefits of exercise-induced inflammation reduction and enhanced vascular elasticity while simultaneously reducing the risk of developing comorbidities and arterial stenosis or occlusion [47].

Considering that the only significant associations in the main analysis and incident sensitivity analyses were those that involved MVPA, it calls into question whether using accelerometer and depressed mood frequency survey data together can help clinicians identify patients who would benefit from remote monitoring, that is, this approach may generate more noise than signal over time. This study only considered a brief (1-week) accelerometer study, and over a year, on average, eclipsed between the *in situ* accelerometer study and the remote mood follow-up survey. Since neither the main analysis (previous stroke cohort) nor the incident sensitivity analyses resulted in significant associations for participants with a previous depression diagnosis, this underscores the need for additional research to determine whether this type of monitoring strategy can generate clinically actionable insights in participants with a previous depression diagnosis. Behavioral monitoring with accelerometer data and self-report surveys may not be helpful in patients with severe, or clinical-grade, depression. Future research should consider large sample sizes, longitudinal study designs, and analyze results stratified by time-to-diagnosis. Relevant to remote monitoring researchers, our findings highlight behavioral differences for those developing exploratory programs and clinically meaningful digital endpoints.

Overall, the cross-sectional analyses offer a robust perspective into the appropriateness of depression monitoring by digital sensors, using accelerometer wristwatches and smartphone, tablet, or PC-linked sensors. These insights offer clinical teams a strategy for translating digital health data, in this case, objective and subjective behavior measures, into scientifically valid frameworks for investigation. Future monitoring of patients at risk of different CeVD types, including those with a previous stroke diagnosis, should expand on our strategy and use both active and passive data to investigate relationships between objective digital sensor data and subsequent mood reports in patients diagnosed with and screened for depression. Based on our exploratory analysis, the potential for longitudinal data from objective sensors to predict mood appears feasible. In addition, PSD researchers should aim to characterize behavior measures linked with depressed mood across defined and clinically meaningful time periods, such as in the 3-month routine monitoring period after a stroke or TIA, considering that observable behaviors may evolve as CeVD or other neurologic disorder pathogenesis progresses.

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Disclaimer

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Data Availability

All data are publicly available, upon research approval access, from UK Biobank [48]. The datasets generated during and analyzed during this study are available from the corresponding author on reasonable request. Analysis code is available [49].

Authors' Contributions

SJZ completed the study design and manuscript drafting. BJE, BMD, and AG provided clinical expertise and contributed to manuscript editing. GMC provided expertise for obtaining data access and designing the study. AG conducted statistical review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions for classifying patients.
[DOCX File, 17 KB - neuro_v4i1e56679_app1.docx]

Multimedia Appendix 2
Sample characteristics across sensitivity cohorts.
[DOCX File, 18 KB - neuro_v4i1e56679_app2.docx]

Multimedia Appendix 3
Ordinal logistic regression assessing objective behavior predictors and depressed mood frequency in the general cohort.
[DOCX File, 15 KB - neuro_v4i1e56679_app3.docx]

Multimedia Appendix 4
Ordinal logistic regression assessing objective behavior predictors and depressed mood frequency in incident stroke cohorts.
[DOCX File, 15 KB - neuro_v4i1e56679_app4.docx]

Multimedia Appendix 5
Ordinal logistic regression assessing objective behavior predictors and depressed mood frequency in incident cerebrovascular disease cohorts.
[DOCX File, 15 KB - neuro_v4i1e56679_app5.docx]

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Abbreviations

BDNF: brain-derived neurotropic factor
CeVD: cerebrovascular disease
DD: depression diagnosis
IC: incident cerebrovascular disease
***ICD-10*:** *International Classification of Diseases, Tenth Revision*
***ICD-11*:** *International Classification of Diseases, Eleventh Revision*
IS: incident stroke
LPA: light physical activity
MADRS: Montgomery–Åsberg Depression Rating Survey
MVPA : moderate-to-vigorous physical activity
OR: odds ratio
PA: physical activity
PHQ-2: Patient Health Questionnaire-2
PSD: poststroke depression

SB: sedentary behavior
TIA: transient ischemic attack
UKBB: UK Biobank

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Exploring Speech Biosignatures for Traumatic Brain Injury and Neurodegeneration: Pilot Machine Learning Study

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Abstract

Background: Speech features are increasingly linked to neurodegenerative and mental health conditions, offering the potential for early detection and differentiation between disorders. As interest in speech analysis grows, distinguishing between conditions becomes critical for reliable diagnosis and assessment.

Objective: This pilot study explores speech biosignatures in two distinct neurodegenerative conditions: (1) mild traumatic brain injuries (eg, concussions) and (2) Parkinson disease (PD) as the neurodegenerative condition.

Methods: The study included speech samples from 235 participants (97 concussed and 94 age-matched healthy controls, 29 PD and 15 healthy controls) for the PaTaKa test and 239 participants (91 concussed and 104 healthy controls, 29 PD and 15 healthy controls) for the Sustained Vowel (/ah/) test. Age-matched healthy controls were used. Young age-matched controls were used for concussion and respective age-matched controls for neurodegenerative participants (15 healthy samples for both tests). Data augmentation with noise was applied to balance small datasets for neurodegenerative and healthy controls. Machine learning models (support vector machine, decision tree, random forest, and Extreme Gradient Boosting) were employed using 37 temporal and spectral speech features. A 5-fold stratified cross-validation was used to evaluate classification performance.

Results: For the PaTaKa test, classifiers performed well, achieving F_1-scores above 0.9 for concussed versus healthy and concussed versus neurodegenerative classifications across all models. Initial tests using the original dataset for neurodegenerative versus healthy classification yielded very poor results, with F_1-scores below 0.2 and accuracy under 30% (eg, below 12 out of 44 correctly classified samples) across all models. This underscored the need for data augmentation, which significantly improved performance to 60% - 70% (eg, 26 - 31 out of 44 samples) accuracy. In contrast, the Sustained Vowel test showed mixed results; F_1-scores remained high (more than 0.85 across all models) for concussed versus neurodegenerative classifications but were significantly lower for concussed versus healthy (0.59 - 0.62) and neurodegenerative versus healthy (0.33 - 0.77), depending on the model.

Conclusions: This study highlights the potential of speech features as biomarkers for neurodegenerative conditions. The PaTaKa test exhibited strong discriminative ability, especially for concussed versus neurodegenerative and concussed versus healthy tasks, whereas challenges remain for neurodegenerative versus healthy classification. These findings emphasize the need for further exploration of speech-based tools for differential diagnosis and early identification in neurodegenerative health.

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KEYWORDS

speech biosignatures; speech feature analysis; amyotrophic lateral sclerosis; ALS; neurodegenerative disease; Parkinson's disease; detection; speech; neurological; traumatic brain injury; concussion; mobile device; digital health; machine learning; mobile health; diagnosis; mobile phone

Introduction

Overview

The fields of health care and medical diagnostics have witnessed a significant shift toward noninvasive and accessible methods for early detection, assessment, and monitoring of medical conditions. This shift has been driven by technological advancements and growing research interest in digital health solutions [1]. Among these, speech analysis has emerged as a promising avenue, with studies identifying speech as a potential biosignature for a variety of neurodegenerative conditions [2,3]. The ability to reliably distinguish between conditions or detect coexisting disorders is critical for accurate diagnosis, tracking disease progression, and evaluating treatment effectiveness [4].

This pilot study investigates speech-based biosignatures of 2 distinct neurodegenerative conditions, that are, neurodegenerative diseases and mild traumatic brain injuries (mTBIs), specifically concussions. Speech patterns often reflect neurodegenerative health, with specific speech features showing promise for distinguishing between these conditions. The dataset includes individuals with concussions, patients with Parkinson disease (PD), and age-matched healthy controls for both groups (15 samples for each test). These groups were selected to ensure demographic compatibility while addressing the unique speech patterns associated with each condition.

Neurodegenerative diseases, such as PD, are characterized by the progressive loss of neurons in the brain and spinal cord, leading to impairments in motor and cognitive functions [5,6]. PD involves the degeneration of dopaminergic neurons, resulting in clinical symptoms such as tremors, rigidity, bradykinesia, and postural instability [7]. These symptoms worsen over time and lack curative treatments, necessitating reliable diagnostic tools for early intervention [8]. On the other hand, concussions, a form of mTBI, result from sudden trauma to the brain, causing temporary cognitive impairments, disruptions in brain function, and neurochemical changes. Repeated concussions are associated with a heightened risk of neurodegenerative disorders, such as dementia, later in life [9]. Despite their prevalence, approximately 90% of concussions go unreported, leading to inadequate medical attention and potentially catastrophic consequences [10].

Traditional diagnostic methods for neurodegenerative diseases and concussions often rely on observable motor symptoms, such as tremors, gait disturbances, or muscle rigidity, as well as subjective assessments of cognitive impairments [11]. However, emerging research has identified speech as a valuable biomarker for neurodegenerative health. Dysarthria and dysphonia, characterized by changes in articulation and motor speech production, are prevalent in both concussions and neurodegenerative conditions like PD [12-14]. Speech features, such as mel frequency cepstral coefficients (MFCCs), jitter, shimmer, harmonics-to-noise ratio (HNR), and other temporal and spectral attributes, have been shown to correlate with underlying neurodegenerative conditions.

In this study, we analyzed speech data from 2 well-established medical speech tasks, the PaTaKa task and the Sustained Vowel task. These tasks are widely used in clinical settings for assessing speech impairments. The objective of this study is to explore the potential of speech features in differentiating between concussions and neurodegenerative conditions, as well as their respective healthy controls, and to assess the feasibility of using these features as biomarkers for diagnosis. By addressing this objective, we aim to contribute to the development of speech-based diagnostic tools for early and accurate identification of neurodegenerative health conditions.

This study evaluated 37 speech-based features (25 temporal and 12 spectral), applying machine learning models such as support vector machine (SVM), decision tree (DT), random forest (RF), and Extreme Gradient Boosting (XGBoost) to classify between the groups.

The remainder of this paper describes our methodology, feature extraction and analysis, machine learning approaches, and results for the binary classification tasks across the 2 speech tests.

Related Work

Diagnosing brain injuries and neurodegenerative diseases can be challenging; for instance, concussions may present subtle features that are difficult to detect, including using third person witness accounts of the injury, clinical examinations, and laboratory testing, where diagnostic accuracy is not always perfect [15]. Recent work has explored the diagnosis of concussions in athletes using mobile technologies [16] and speech analysis [17,18], while digital assessments, coupled with speech analysis, are also increasingly being used for individuals with neurodegenerative diseases [19]. In a study by Tsanas [19], various speech tasks have been used to distinguish between healthy people and individuals with PD, with relatively high accuracy. Other previous research has investigated the overall symptom severity of individuals with a neurodegenerative condition [11,20], the effectiveness of voice rehabilitation [21], and how to distinguish PD from other conditions such as essential tremor or atypical parkinsonism [22].

The choice of speech task is critical to obtaining speech samples that can be used for subsequent feature extraction and analysis. One commonly used speech task is to ask an individual to produce sustained phonation of vowels. For instance, the study by Mallela et al [23] presents an automatic voice assessment approach for separating healthy individuals from patients with amyotrophic lateral sclerosis (ALS). Although our study focuses exclusively on PD as the representative neurodegenerative condition, references to ALS studies are included to highlight the broader research landscape on neurodegenerative speech biosignatures and their diagnostic significance. Linear discriminant analysis is used to classify phonation, with the most successful model achieving more than 90% accuracy. Similarly, a study by Rueda and Krishnan [24] obtained sustained vowel data from 57 PD patients and 57 healthy individuals, and the study used 5 hierarchical and 1 partition-based clustering techniques to compare and cross-check PD patients at different phases. In some cases, researchers have relied on existing voice recordings, for example, obtained through the Parkinson's Voice Initiative project (the largest speech-PD dataset so far) to analyze voice impairment due to PD [25].

Daudet et al [18] developed a mobile app to diagnose concussions, using data from 47 high-schools and colleges in the Midwest. The study used several speech tasks such as repetition of a sequential motion rate, alternating motion rate, multisyllabic words (words with 4 syllables containing front, middle, and back vowels, and bilabial, alveolar, velar, and glide consonants). The work by Vashkevich et al [26] presented features for detecting pathological changes in acoustic speech signals for ALS diagnosis. It used recordings from 48 people (26 with ALS) and investigated vowel harmony. The features obtained an 88% correct classification performance using linear discriminant analysis. Various speech-based indicators, such as shimmer, jitter, HNR, and other temporal and spectral indicators, have also been explored as dysphonia measures in individuals with neurodegenerative diseases [27]. Finally, in a study by Benba et al [22], the authors investigated the most effective acoustic elements for accurately identifying symptoms of PD, combining shimmer, jitter, pitch, harmonicity, pulses, and voicing by using K-Nearest Neighbor classifiers with different types of kernels (ie, radial basis functions, linear, polynomial, and multilayer perceptron).

Machine learning–based solutions have become the standard for most health care decision-making processes, for example, most previous works focus on differentiating diseased individuals from healthy controls. For example, the work by Tsanas and Arora [28] evaluated 2289 individuals (2023 healthy controls and 246 PD patients) and analyzed 15,227 voice tasks (9994 for healthy controls and 5233 for PD patients). Similarly, the work Bongioanni [29] compared speech-based automatic classification of patients with ALS and healthy people using sustained phoneme generation, diadochokinetic task, and spontaneous speech. They classified voice samples from 25 patients with ALS and 25 healthy participants using SVMs and deep neural networks. More recently, more focus has been given to multiclass scenarios, for example, the study by Benba et al [22] used a Convolutional Neural Network Long Short-term Memory to categorize ALS, PD, and healthy controls. The study analyzed speech data from 60 people, focusing on sentence reading, sound repetition, and sustained vowels.

Though there are studies that had investigate speech features pertaining to neurodegenerative disorders or acquired neurodegenerative disorders like mTBI, there are not many studies exploring speech feature variations between those populations which might co-occur and impact speech production differently.

The aim of this study is to investigate whether distinct speech-based biomarkers, derived from commonly used tasks like the PaTaKa and Sustained Vowel tests, can effectively differentiate between concussed individuals, neurodegenerative conditions (focused on PD), and healthy controls.

Methods

Data Collection

This study focused on 2 widely used speech tasks, the sequential motion rate task (PaTaKa test) and the Sustained Vowel test. The PaTaKa test evaluates speech-motor function by asking participants to take a deep breath and repeatedly articulate “Pa-Ta-Ka” as steadily as possible in 1 breath, providing insights into the rate and precision of sequential articulatory actions.

In the Sustained Vowel test, participants were instructed to sustain the vowel sound “ah” for as long as possible, offering valuable information about voice quality and potential vocal tremor. Both tasks were assigned to four participant groups, that are (1) individuals with concussions, (2) individuals with neurodegenerative conditions (specifically PD), (3) healthy controls age-matched to the concussed group, and (4) healthy controls age-matched to the neurodegenerative group.

Individuals diagnosed with a concussion were evaluated by physicians or athletic trainers using standardized neurocognitive assessment tools, such as ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) by ImPACT Applications, Inc, SCAT (Sport Concussion Assessment Tool), an open-access tool , and SAC (Standardized Assessment of Concussion) by researchers at the University of North Carolina’s Sports Medicine Research Laboratory, within 48 hours of the suspected injury. Individuals with neurodegenerative conditions (ie, PD) were diagnosed by licensed neurologists or family physicians. All participants with PD were in the early stages of disease progression (Hoehn and Yahr stage 1 - 2) and were assessed using tools such as the MDS-UPDRS (Movement Disorder Society - Unified Parkinson’s Disease Rating Scale) and Hoehn and Yahr Scale.

Healthy controls were divided into two groups: (1) young healthy individuals age-matched to the concussed group and (2) older healthy individuals age-matched to the neurodegenerative group. This separation ensures more accurate comparisons between the groups, minimizing the confounding effects of age-related speech differences.

Participants completed the speech tasks using a mobile app (smartphone or tablet) that provided both visual and auditory instructions. The app also recorded the audio samples digitally for subsequent analysis. Audio data were collected from a total of 235 and 239 participants for the PaTaKa and Sustained Vowel tests, respectively, as shown in Table 1.

Table . Description of collected samples.

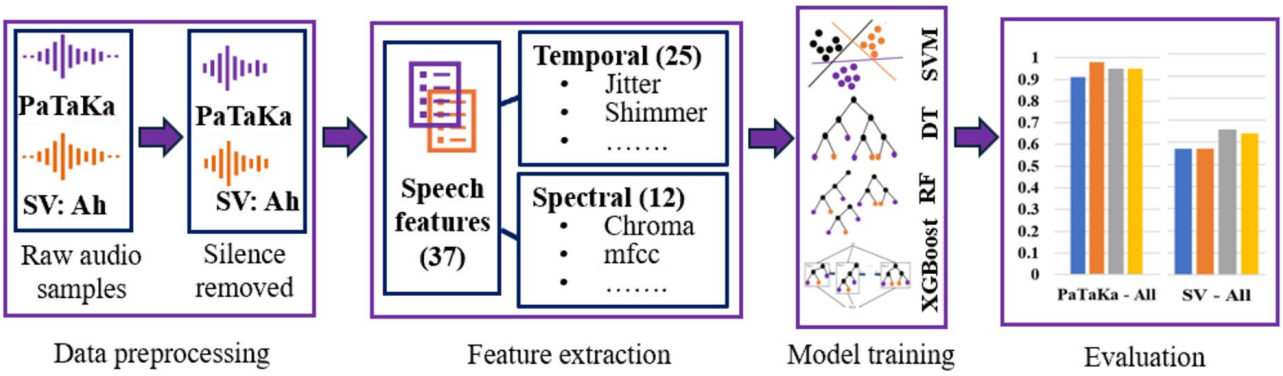
Test name and population		Samples, n	Sex		Age (years), mean (SD)
			Male, n	Female, n	
PaTaKa					
	Concussed	97	86	11	17 (3)
	Healthy control (young)	94	81	13	17 (3)
	Neurodegenerative (PD[a])	29	17	12	63.67 (4.95)
	Healthy control (older)	15	5	10	63.67 (4.95)
Sustained Vowel					
	Concussed	91	82	9	17 (3)
	Healthy control (young)	104	90	14	17 (3)
	Neurodegenerative (PD)	29	17	12	63.67 (4.95)
	Healthy control (older)	15	5	10	63.67 (4.95)

[a]PD: Parkinson disease.

The PaTaKa test dataset includes speech samples from 97 concussed participants, 29 participants with neurodegenerative conditions (ie, PD), 97 age-matched young healthy controls, and 15 age-matched older healthy controls. Similarly, the Sustained Vowel dataset consists of speech samples from 91 concussed participants, 29 participants with neurodegenerative conditions (ie, PD), 91 age-matched young healthy controls, and 15 age-matched older healthy controls.

In the remainder of this section, we describe the 4 key components of the proposed analysis methodology, shown in Figure 1, that are data preprocessing, feature extraction, model training, and evaluation.

Figure 1. Overall visualization of the 4 methodological steps: data preprocessing, feature extraction, model training, evaluation. DT: decision tree; mfcc: mel frequency cepstral coefficient; RF: random forest; SV: Sustained Vowel; SVM: support vector machine; XGBoost: Extreme Gradient Boosting.



Data Preprocessing

The voiced portions of speech signals typically carry the most critical information for analysis. Therefore, to enhance the quality and efficiency of feature extraction, it is essential to eliminate unnecessary components, such as silence intervals and extraneous noise, during the preprocessing phase. In this study, silence intervals were removed at 2 points in each speech recording using the free software developed by Muse group named “Audacity”. Specifically, silence was cut from the beginning of the recording to the onset of vocalization and from the offset of vocalization to the end of the recording.

In addition, recordings that did not meet the study’s requirements, such as those where participants failed to produce the expected utterances (eg, “PaTaKa” in 1 continuous breath or sustained vowel production without interruptions), were excluded from further analysis. This step ensured a high-quality dataset for feature extraction and classification, thereby improving the reliability of the results.

Data Augmentation

To address the challenges of imbalanced datasets and improve classification performance, data augmentation was applied to specific data subsets, particularly those with limited samples, such as the neurodegenerative (ie, PD) and age-matched healthy datasets. The augmentation process involved adding Gaussian noise to the raw audio signals. The noise factor was set to 0.005 to ensure that the original speech characteristics were preserved

while introducing subtle variations to increase sample diversity. For each audio file, a noise vector was generated using a Gaussian distribution, scaled by the specified noise factor, and added to the original signal. The augmented audio signals were then normalized to ensure they remained within the acceptable amplitude range for further processing.

This step increased the dataset size from 29 PD and 15 healthy samples to 58 PD and 30 healthy samples, resulting in a notable improvement in classification accuracy from under 30% (original data) to 60% - 70% (augmented data).

Feature Extraction

Feature extraction is the process of transforming raw audio data into numerical features while retaining the critical information embedded within the original signal. Among various methods for converting speech into numerical data, temporal and spectral features are widely used in speech-processing research [22,26,27,30]. In these studies, both types of features were extracted using Python's Librosa library [31].

Temporal features describe the changes in an audio signal over time, such as amplitude and pitch variation. This study extracted 25 temporal features, including 4 fundamental frequency measures (eg, mean and SD of F0), 5 jitter measures, 6 shimmer measures, and the HNR. These features provide insights into voice quality and stability, commonly associated with motor speech dysfunctions. The full list and descriptions of these temporal features are provided in Multimedia Appendix 1.

Spectral features analyze the frequency components of the speech signal and are commonly used in applications such as speech recognition and speaker identification. This study extracted 12 spectral features, including MFCC, spectral centroid, chroma features, and spectral flatness. These features capture frequency-domain characteristics that are sensitive to articulation and vocal tract configurations. Detailed descriptions of these spectral features are presented in Multimedia Appendix 1.

All 37 extracted features (25 temporal and 12 spectral) were included in the training and evaluation of machine learning models. By retaining the full feature set, we ensured that potentially valuable information was preserved, particularly given the small sample size. Data augmentation techniques, such as adding noise to the audio samples, were used to improve the robustness of the models and enhance performance, especially for the classification between neurodegenerative and healthy controls, where the original dataset resulted in poor classification performance.

Model Training

In recent years, the trend in digital health care has been to use machine learning models to classify input data (speech samples) into 2 or more classes based on extracted features. In this work, we employed several popular machine learning techniques, such as SVM, DT, RF, and XGBoost [18]. These models were chosen due to their interpretability, robustness, and ability to handle small datasets effectively, which is essential for clinical applications.

SVM, a supervised learning algorithm proposed by Boser et al [32], is grounded in statistical learning theory and is particularly effective for high-dimensional data [33]. It uses hyperplanes and margins to separate data into classes, with its performance being highly dependent on data scaling and the choice of kernel functions. DTs, on the other hand, divide feature space into regions by recursively splitting data and assigning classes to leaf nodes [34]. Despite their simplicity, DTs are prone to overfitting, especially on small datasets.

RFs mitigate this issue by employing an ensemble of DTs trained on bootstrapped datasets, with each tree built using a random subset of features [35]. The final class prediction is based on a majority vote across all trees, which reduces variance and enhances model robustness. Finally, XGBoost, a gradient boosting implementation, constructs DTs sequentially, optimizing performance by correcting errors from previous iterations [36]. It is known for its computational efficiency and scalability, making it a popular choice for structured datasets. For a given sample, the final prediction can be calculated by summing up the scores of overall leaves, which is illustrated in Multimedia Appendix 2.

Given the limited size of our dataset, we prioritized traditional machine-learning models over deep learning methods. While deep learning algorithms have demonstrated exceptional performance on large datasets, their effectiveness diminishes with smaller datasets due to overfitting and computational requirements. Traditional machine learning models, such as SVM and RF, offer superior interpretability, which is critical for clinical decision-making [28]. For instance, the study by Pishgar et al [37] found that on a small voice disorder dataset, SVM outperformed a deep neural network in terms of sensitivity and specificity.

In this study, all 37 extracted features (25 temporal and 12 spectral) were used without any feature selection or filtering. Data augmentation was applied to address the limited sample size, particularly for the neurodegenerative versus healthy dataset, where the augmented dataset improved model performance.

To train and evaluate the machine learning models, we applied a 75 - 25 stratified split of the dataset into training and test sets, ensuring that class distributions were preserved. Stratified 5-fold cross-validation was used to evaluate model performance more reliably, and Grid Search was used to fine-tune hyperparameters for all algorithms.

Evaluation

In this study, we assessed the performance of our classification models using multiple evaluation metrics, with a particular focus on the F_1-score due to its robustness in handling unbalanced datasets. The F_1-score is particularly well-suited for situations where there is an imbalance in the class distribution, as it provides a harmonic mean of precision and recall, balancing the trade-off between these 2 metrics. The F_1-score is defined as follows in Multimedia Appendix 2.

Both precision and recall are crucial in medical applications, where the consequences of false positives or false negatives can

be severe. The F_1-score offers a balanced view of a model's performance when neither precision nor recall can be prioritized over the other. A higher F_1-score (ranging from 0 to 1) indicates a better-performing model.

In addition to the F_1-score, we evaluated our models using precision, recall, and accuracy to provide a comprehensive view of model performance. These metrics helped compare the performance of models across different speech tasks (PaTaKa and Sustained Vowel) and combinations (eg, concussed vs healthy, concussed vs neurodegenerative, neurodegenerative vs healthy). The results section discusses these findings in detail, highlighting the implications of our model's performance for clinical applications.

Ethical Considerations

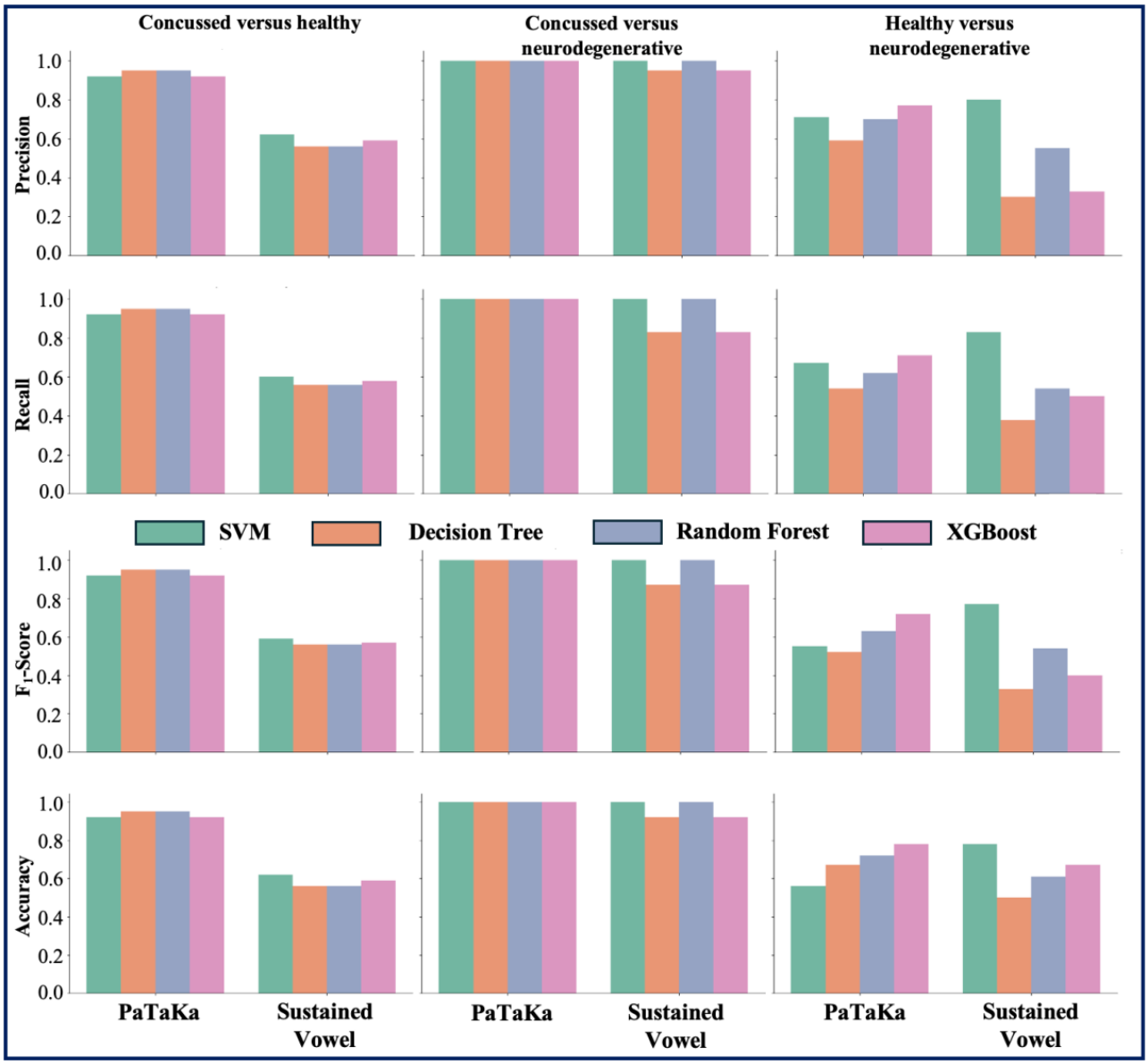
This research was conducted in compliance with ethical standards and approved by the Institutional Review Board at the University of Notre Dame. The approval numbers for this study are 18-01-4338 and 18-01-4340 for PD and concussion, respectively. All participants provided informed consent (Multimedia Appendices 3 and 4), and their confidentiality was ensured throughout the study.

Results

Overview

The performance of the models was evaluated using precision, recall, F_1-score, and accuracy across 3 participant combinations (ie, concussed vs healthy, concussed vs neurodegenerative, and neurodegenerative vs healthy) for 2 widely used speech tasks, PaTaKa and Sustained Vowel. The results provide insights into the discriminative ability of each test and highlight the comparative effectiveness of different classifiers in distinguishing between participant groups. While the PaTaKa task generally demonstrated robust performance across all combinations, the Sustained Vowel test showed varying levels of accuracy, particularly for certain groups and classifiers. The performance for each combination and test, along with discussions on their implications are illustrated in Figure 2.

Figure 2. Performance metrics by test type, model, and combination. SVM: support vector machine; XGBoost: Extreme Gradient Boosting.



Concussed Versus Healthy

PaTaKa Test

The models performed exceptionally well, achieving near-perfect precision, recall, F_1-score, and accuracy across all classifiers. DT and RF slightly outperformed SVM and XGBoost, consistently achieving 0.95. There are no sources in the current document across all metrics. These results highlight the PaTaKa test's robustness in distinguishing between concussed and healthy participants.

Sustained Vowel Test

Performance dropped significantly compared with the PaTaKa test. SVM and XGBoost achieved slightly higher metrics, with F_1-scores around 0.59 - 0.62. DT and RF had the lowest performance, with metrics around 0.56. The reduced performance might indicate that sustained vowels are less effective for distinguishing concussed participants from healthy individuals.

Concussed Versus Neurodegenerative

PaTaKa Test

All models performed perfectly, achieving precision, recall, F_1-score, and accuracy of 1.0. This demonstrates the effectiveness of the PaTaKa test for differentiating concussed participants from those with neurodegenerative conditions. Consistency across all classifiers reinforces the reliability of this task for this combination.

Sustained Vowel Test

Similar to the PaTaKa test, most models achieved perfect scores across all metrics. However, DT and XGBoost showed slightly reduced performance, with F_1-scores of 0.87 and accuracy of 0.92. Despite slight variability, the Sustained Vowel test remains a strong indicator for distinguishing these groups.

Neurodegenerative Versus Healthy

PaTaKa Test

Results varied significantly across classifiers. RF and XGBoost outperformed others, achieving F_1-scores of 0.63 and 0.72, respectively. DT and SVM performed poorly, with F_1-scores around 0.52 - 0.55. These results indicate that the PaTaKa test has moderate effectiveness for this group but requires careful classifier selection.

Sustained Vowel Test

Similar trends were observed. XGBoost achieved the highest F_1-score (0.40) and accuracy (0.67), while other models showed significantly lower performance. This underscores the challenge of distinguishing neurodegenerative participants from healthy controls using sustained vowel tasks.

Feature Set Analysis

Understanding the importance of individual features in classification tasks is crucial for interpreting the predictive power of machine learning models. In this study, we examined feature importance across all tests and combinations to identify the most influential speech features contributing to the classification of concussed, neurodegenerative, and healthy individuals. Feature importance was calculated for each model (SVM, DT, RF, and XGBoost) using a combination of metrics, such as Gini importance, SHAP values, or permutation importance, depending on the model.

To identify globally significant features, we analyzed the frequency of features ranked among the top 5 across all 24 tests. A summary of the top 10 most frequent features is presented in Table 2, while Table 3 provides combination-specific feature importance values. The most frequently identified features were temporal and spectral characteristics, which are known to capture both short-term and long-term speech patterns.

Table . Top 10 most frequent features across all tests.

Rank	Feature	Frequency	Mean importance
1	duration	15	0.29
2	zero_crossing_rate	13	0.33
3	spectral_flatness	12	0.30
4	mfcc[a]	11	0.25
5	spectral_bandwidth	7	0.42
6	spectral_centroid	6	0.07
7	spectral_contrast	5	0.07
8	chroma_stft	5	0.32
9	HNR[b]	4	0.06
10	f4_median	4	0.04

[a]mfcc: mel frequency cepstral coefficient.

[b]HNR: harmonics-to-noise ratio.

Table . Combination specific feature importance value.

Combination and test		Feature	Value
Concussed versus healthy			
	PaTaKa	Duration	1.9
	PaTaKa	Zero-crossing rate	0.47
	Sustained Vowel	Spectral flatness	0.12
Concussed versus neurodegenerative			
	PaTaKa	Spectral bandwidth	1.3
	Sustained Vowel	MFCC[a]	2.9
Neurodegenerative versus healthy			
	PaTaKa	HNR[b]	0.43
	Sustained Vowel	Spectral flatness	0.76

[a]MFCC: mel frequency cepstral coefficient.

[b]HNR: harmonics-to-noise ratio.

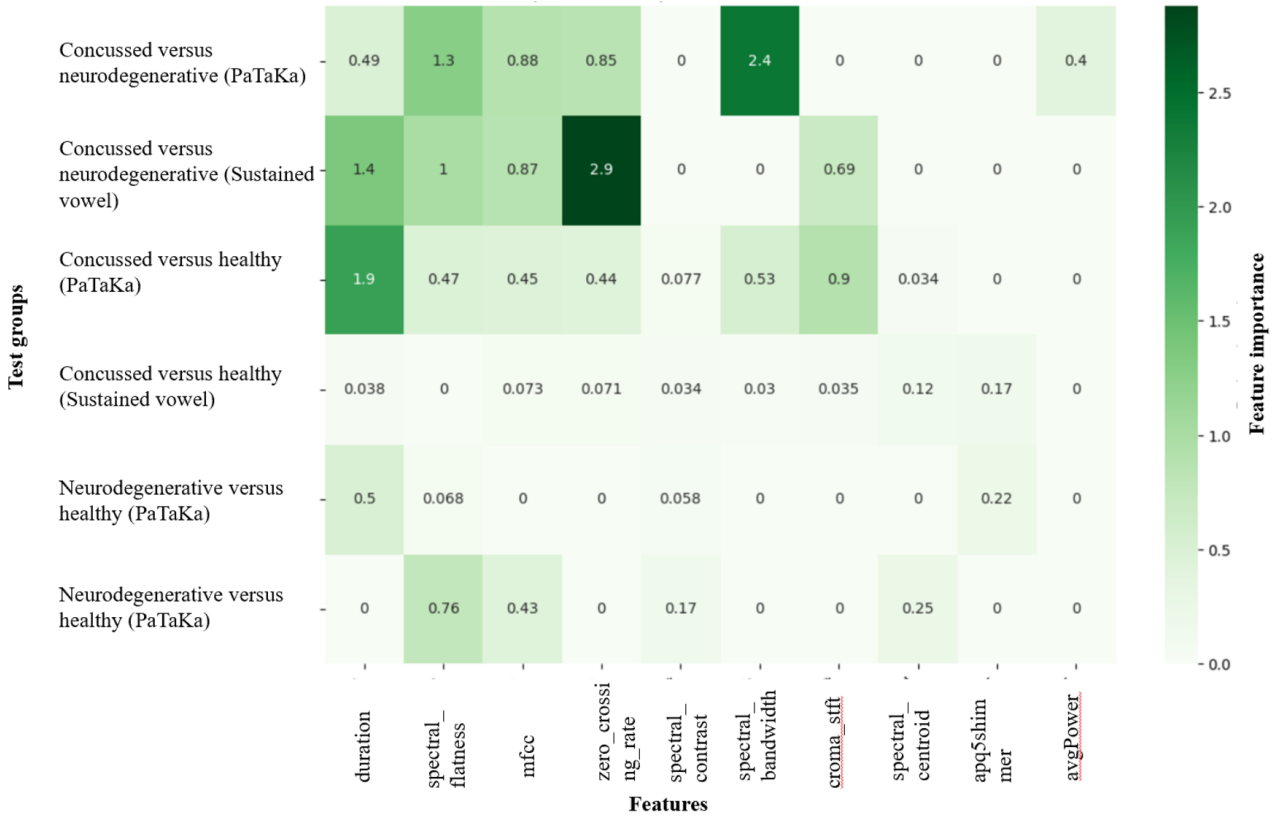
Among the top 10 features, duration, zero-crossing rate, and spectral_flatness were the most influential, appearing consistently across multiple tests and combinations. These features reflect critical aspects of speech production, including articulation rate, periodicity, and frequency smoothness. For instance:

- Duration: This feature provides insights into motor control and speech articulation by measuring the length of utterances.
- Zero-crossing rate: Indicative of voice signal periodicity, this feature is particularly significant in distinguishing voiced and unvoiced speech segments.
- Spectral_flatness: This feature quantifies the uniformity of the speech spectrum, distinguishing between harmonic and noise-like components.

Combination-specific patterns further highlight the variability in feature importance depending on the test (PaTaKa or Sustained Vowel) and the target classification task (concussed vs healthy, concussed vs neurodegenerative, and neurodegenerative vs healthy). For example, (1) in the concussed versus healthy classification, features like mfcc and spectral bandwidth were highly impactful, particularly in the PaTaKa test, (2) in the Concussed concussed versus neurodegenerative classification, spectral_centroid and chroma_stft played a significant role in distinguishing between the 2 groups, and (3) for the neurodegenerative versus healthy classification, features such as f4_median and HNR were key discriminators, particularly in the Sustained Vowel test.

The distribution of feature importance values across combinations and tests is visualized in Figure 3, while the detailed numerical values for each combination and test are available in Table 3. These findings emphasize the variability of feature contributions across different tasks and highlight the importance of task-specific feature analysis for robust classification.

Figure 3. Top 10 most frequent features across all tests. mfcc: mel frequency cepstral coefficients.



Discussion

Principal Findings

The findings of this study provide valuable insights into the use of speech-based features for differentiating between neurodegenerative conditions, particularly mTBI (concussions) and neurodegenerative diseases (eg, PD). By leveraging 2 commonly used speech tasks, the PaTaKa test and the Sustained Vowel test, and a variety of machine learning models, we achieved classification accuracies ranging from 60% to 90%, with RF and XGBoost models consistently outperforming others. In addition, we identified key speech features, such as duration, zero-crossing rate, and spectral flatness, as critical biomarkers for distinguishing between these conditions. These results underscore the potential of speech features as noninvasive biomarkers for neurodegenerative health assessment and highlight the complementary roles of the PaTaKa and Sustained Vowel tests in revealing task-specific and globally significant features.

Key Observations

First, task-specific performance. The PaTaKa test consistently outperformed the Sustained Vowel test across all combinations. This may be attributed to the sequential articulatory movements required in the PaTaKa test, which can better capture subtle motor and speech deficits. For example, in the concussed versus healthy classification, F_1-scores for PaTaKa exceeded 0.9 across all models, whereas the Sustained Vowel test achieved F_1-scores below 0.6 for the same classification. These findings highlight the importance of task selection in speech analysis and suggest that diadochokinetic tasks may provide richer diagnostic information.

Second, model-specific trends. Among the machine learning models, RF and XGBoost consistently performed well, demonstrating their ability to handle complex, nonlinear relationships in speech data. This aligns with previous research highlighting the robustness of ensemble learning methods in biomedical and speech signal processing tasks [38].

Third, the high interpretability of DTs also provides an advantage for clinical applications, particularly in scenarios where transparency is critical for adoption in health care settings.

Fourth, despite its slightly lower performance in some scenarios, DT models remain valuable due to their simplicity and ease of implementation.

Fifth, interestingly, SVMs displayed strong performance in balanced datasets, particularly in the concussed versus neurodegenerative classification, where precision and recall consistently reached 1.0 for the PaTaKa test. This finding is consistent with previous studies showing that SVMs are effective for high-dimensional data, especially when datasets are carefully preprocessed and balanced [39]. The performance of SVM in this classification task further underscores its utility in distinguishing nuanced differences between distinct neurodegenerative conditions using speech features.

Finally, feature importance. The analysis of feature importance revealed that a small subset of features consistently played a dominant role across tests and combinations. Temporal features such as duration and zero-crossing rate were particularly influential, likely reflecting disruptions in motor control and

speech rhythm caused by both concussions and neurodegenerative conditions. Spectral features, including spectral_flatness, mfcc, and spectral_bandwidth, were also critical, highlighting their utility in capturing frequency-domain variations associated with speech pathologies. These results align with previous research, which has emphasized the role of both temporal and spectral features in detecting neurodegenerative impairments.

Comparison With Previous Studies

Our findings corroborate and extend existing literature on speech-based biomarkers for neurodegenerative conditions. Previous research has demonstrated the utility of features such as MFCC and jitter for detecting PD [4], as well as features like zero-crossing rate and duration for identifying concussions [19]. However, this study uniquely emphasizes the differentiation between neurodegenerative diseases like PD and mild traumatic brain injury (eg, concussions), a task that remains relatively underexplored in existing literature.

Furthermore, the inclusion of both PaTaKa and Sustained Vowel tests enables a more comprehensive analysis of task-specific feature relevance. While previous studies have evaluated the diagnostic utility of individual speech tasks (eg, sustained phonation for ALS in studies by Allison et al [13] and Tsanas et al [27]), this work highlights how combining multiple tasks can reveal unique and complementary insights into speech biosignatures associated with diverse neurodegenerative conditions.

In addition to confirming the significance of widely used features such as spectral flatness and zero-crossing rate, our study identifies new combinations of features, including spectral contrast and chroma-based features, as being critical for distinguishing between these groups. These results align with recent advancements in the field, where ensemble learning models, such as RF and XGBoost, are increasingly used to capture the intricate, nonlinear relationships within speech data [23].

By addressing age-related variability and introducing data augmentation to mitigate the challenges of limited datasets, this study not only validates previously established findings but also sets the stage for future research aimed at improving the diagnostic accuracy of speech-based assessments across distinct but potentially overlapping neurodegenerative conditions.

Implications for Clinical Practice

The results of this study highlight several practical implications for clinical applications.

First, noninvasive diagnostics. The reliance on speech features, which can be collected using readily available devices like smartphones, opens up possibilities for remote and noninvasive diagnostics. This is particularly valuable in resource-constrained settings where access to advanced imaging or neurophysiological tests may be limited.

Second, early detection. The ability to detect subtle speech impairments associated with neurodegenerative conditions could enable earlier diagnosis, allowing for timely interventions.

Finally, task selection. The superior performance of the PaTaKa test suggests that it should be prioritized in future speech-based diagnostic protocols, particularly for distinguishing between concussions and neurodegenerative conditions.

Limitations

Despite the promising results, there are several limitations to this study.

First, small dataset—the dataset size, particularly for neurodegenerative diseases, was relatively small. This may limit the generalizability of the findings to larger, more diverse populations.

Second, demographic differences—the age gap between the concussed (younger) and neurodegenerative (older) populations poses a potential confounding factor. While age-matched healthy controls were included, the results could be influenced by inherent age-related differences in speech production.

Third, feature engineering and contextual factors—while the study identified important features, the reliance on manual feature extraction may overlook nuanced patterns. Advanced techniques, such as deep learning–based feature discovery, could reveal hidden characteristics in speech data. Future research should also account for comorbidities and age-related factors, as these can influence speech biosignatures and potentially confound results. Age-normalized datasets and statistical adjustments can further enhance the robustness of classification models.

Future Directions

This study demonstrates the potential of speech-based features to differentiate between concussed, neurodegenerative, and healthy individuals. While promising, the findings also highlight several areas for improvement and expansion, which we aim to address in future work.

First, dataset expansion and diversity. The current dataset includes limited samples from each group, particularly for neurodegenerative diseases. Future studies will expand the dataset to include larger and more diverse populations, ensuring broader generalizability of the results. In addition, we aim to achieve a more balanced age distribution across all participant groups, enabling more robust analyses and minimizing potential biases.

Second, age-related effects. While we mitigated some confounding effects of age by including 2 distinct healthy control groups (age-matched for concussed and neurodegenerative participants), future studies will incorporate more advanced strategies to address age-related variations in speech features. These include (1) explicitly including age as a covariate in statistical models to control its effects and quantify its influence on the results, (2) conducting age-matched subgroup analyses to validate that classification performance is not driven by age-related biases but by the underlying neurodegenerative conditions, and (3) expanding the dataset to improve the representation of younger and older age groups across all conditions.

Third, feature engineering and discovery. While this study focused on predefined temporal and spectral features, advanced deep learning models such as autoencoders or transformer-based models could uncover latent features that may better distinguish between neurodegenerative conditions. In addition, further exploration of task-specific feature relevance could reveal complementary insights into speech patterns for different health conditions.

Fourth, longitudinal data analysis. Future work should explore longitudinal data to track changes in speech biosignatures over time. This would help identify temporal patterns associated with disease progression and recovery, providing valuable insights for monitoring treatment efficacy and early diagnosis.

Fifth, integration with clinical practice. To enhance the clinical utility of this research, future efforts should focus on integrating speech-based diagnostic tools into real-world health care settings. This includes (1) developing user-friendly mobile apps or web applications for noninvasive speech analysis and (2) collaborating with clinicians to validate the models and evaluate their effectiveness in clinical decision making processes.

Finally, evaluation metrics and benchmarking. Expanding the evaluation metrics to include area under the receiver operating characteristic curve and precision-recall curves would provide a more comprehensive understanding of model performance. In addition, benchmarking against existing speech-based models or alternative diagnostic tools could further contextualize the findings and demonstrate the added value of the proposed methods.

By addressing these areas, future research can build upon the findings of this study to further advance the field of speech analysis in neurodegenerative health, improve diagnostic accuracy, and pave the way for noninvasive, scalable diagnostic tools.

Conclusion

This study demonstrates the potential of speech features, particularly those derived from the PaTaKa test, as effective biomarkers for distinguishing between concussed, neurodegenerative, and healthy individuals. By identifying task-specific and globally important features, the findings lay the groundwork for developing noninvasive, speech-based diagnostic tools that can be readily implemented in clinical practice. Further research addressing the study's limitations could pave the way for broader applications of speech analysis in neurodegenerative health.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Feature description.
[DOCX File, 17 KB - neuro_v4i1e64624_app1.docx]

Multimedia Appendix 2
Equations.
[DOCX File, 15 KB - neuro_v4i1e64624_app2.docx]

Multimedia Appendix 3
Consent form for participants with neurodegenerative conditions.
[PDF File, 76 KB - neuro_v4i1e64624_app3.pdf]

Multimedia Appendix 4
Consent form for participants with concussions.
[PDF File, 76 KB - neuro_v4i1e64624_app4.pdf]

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Abbreviations

ALS: amyotrophic lateral sclerosis
DT: decision tree
HNR: harmonics-to-noise ratio
ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing
MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MFCC: mel frequency cepstral coefficient
mTBI: mild traumatic brain injury
PD: Parkinson disease
RF: random forest
SAC: Standardized Assessment of Concussion
SCAT: Sport Concussion Assessment Tool
SVM: support vector machine
XGBoost: Extreme Gradient Boosting

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Effectiveness of Artificial Intelligence–Based Platform in Administering Therapies for Children With Autism Spectrum Disorder: 12-Month Observational Study

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Abstract

Background: A 12-month longitudinal observational study was conducted on 43 children aged 2 - 18 years to evaluate the effectiveness of the CognitiveBotics artificial intelligence (AI)–based platform in conjunction with continuous therapy in improving therapeutic outcomes for children with autism spectrum disorder (ASD).

Objective: This study evaluates the CognitiveBotics software's effectiveness in supporting children with ASD through structured, technology-assisted learning. The primary objectives include assessing user engagement, tracking progress, and measuring efficacy using standardized clinical assessments.

Methods: A 12-month observational study was conducted on children diagnosed with ASD using the CognitiveBotics AI-based platform. Standardized assessments, include the Childhood Autism Rating Scale (CARS), Vineland Social Maturity Scale, Developmental Screening Test, and Receptive Expressive Emergent Language Test (REEL), were conducted at baseline (T1) and at the endpoint (T2). All participants meeting the inclusion criteria were provided access to the platform and received standard therapy. Participants who consistently adhered to platform use as per the study protocol were classified as the intervention group, while those who did not maintain continuous platform use were designated as the control group. Additionally, caregivers received structured training, including web-based parent teaching sessions, reinforcement strategy training, and home-based activity guidance.

Results: Participants in the intervention group demonstrated statistically significant improvements across multiple scales. CARS scores reduced from 33.41 (SD 1.89) at T1 to 28.34 (SD 3.80) at T2 (P<.001). Social age increased from 22.80 (SD 7.33) to 35.76 (SD 9.09; mean change: 12.96, 56.84% increase; P<.001). Social quotient increased from 53.26 (SD 11.84) to 64.75 (SD 16.12; mean change: 11.49, 21.57% increase; P<.001). Developmental age showed an improvement from 30.93 (SD 9.91) to 45.31 (SD 11.20; mean change: 14.38, 46.49% increase; P<.001), while developmental quotient increased from 70.94 (SD 10.95) to 81.33 (SD 16.85; mean change: 10.39, 14.65% increase; P<.001). REEL scores showed substantial improvements, with receptive language increasing by 56.22% (P<.001) and expressive language by 59.93% (P<.001). In the control group, while most psychometric parameters showed some improvements, they were not statistically significant. CARS scores decreased by 10.62% (P=.06), social age increased by 52.27% (P=.06), social quotient increased by 19.62% (P=.12), developmental age increased by 44.88% (P=.06), and developmental quotient increased by 11.23% (P=.19). REEL receptive and expressive language increased by 34.69% (P=.10) and 40.48% (P=.054), respectively.

Conclusions: Overall, the platform was an effective supplement in enhancing therapeutic outcomes for children with ASD. This platform holds promise as a valuable tool for augmenting ASD therapies across cognitive, social, and developmental domains. Future development should prioritize expanding the product's accessibility across various languages, ensuring cultural sensitivity and enhancing user-friendliness.

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KEYWORDS

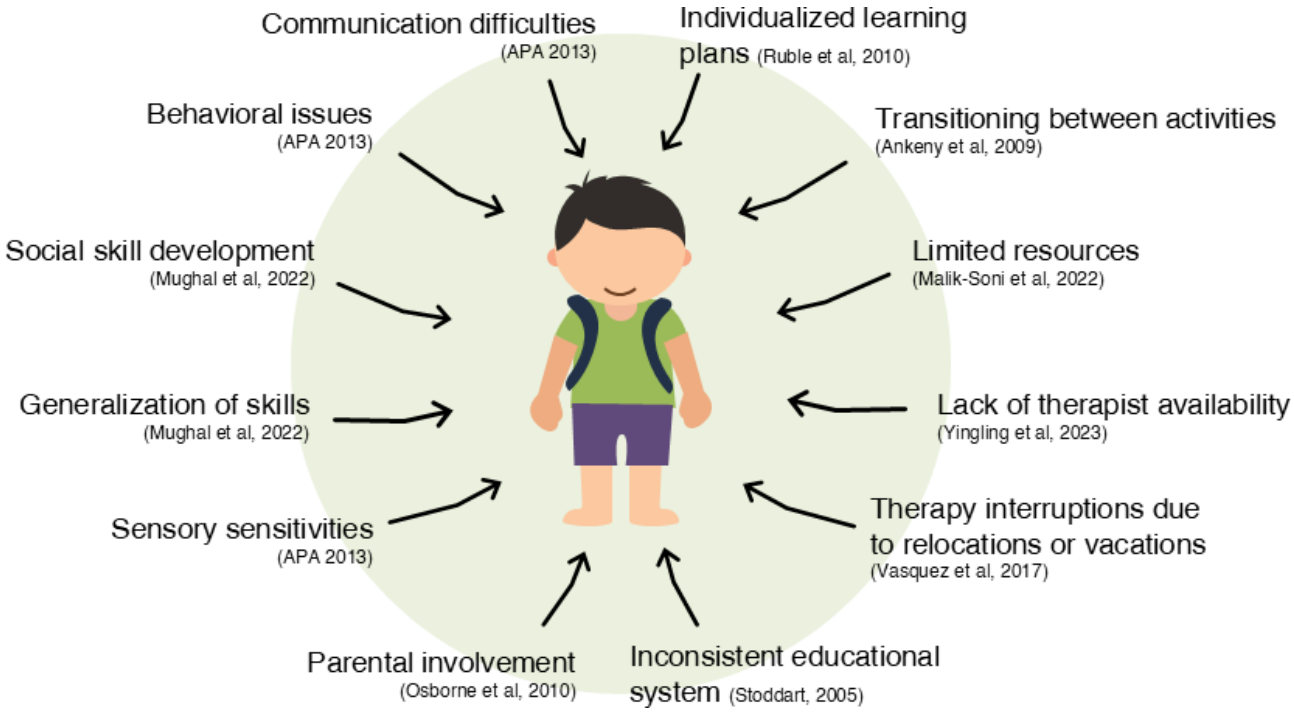
autism spectrum disorder; neurodevelopmental disorders; applied behavior analysis; software; artificial intelligence

Introduction

Autism, otherwise known as autism spectrum disorder (ASD), is a neurodevelopmental disorder with a wide continuum of associated cognitive and neurobehavioral deficits including, but not limited to, 3 core defining features: impairments in social interaction and impairments in verbal and nonverbal communication, combined with restricted and repetitive patterns of behaviors [1]. Such impairments can impede an individual's social level of interaction, learning aptitude, and employability, leading to poor long-term outcomes, difficulties in socializing, poor job performance, and difficulties in activities of daily living [2-5]. The estimated prevalence of ASD has increased from 1 in 10,000 in the 1960s to at least 1 in 36 today [6,7].

The cause for the rise of children diagnosed with ASD is unknown [8]. What is clear is that early and consistent intervention is crucial for positive long-term outcomes [9]. Currently, there are no medical treatments that can effectively cure individuals with ASD, with most interventions involving applied behavioral analysis (ABA), speech and language therapy, and sensory integration to address the core symptoms of ASD [10,11]. To provide adequate and quality therapy to children with autism, a team of trained professionals ranging from pediatricians, child psychiatrists; occupational, behavioral, and speech therapists; psychologists, specialist teachers, and dedicated caregivers are necessary [12]. Providing therapy to children with autism can be rewarding but challenging due to several factors. Figure 1 provides an insight into the challenges faced by the stakeholders in the care and support of children with autism [13-20].

Figure 1. Challenges in providing therapy to individuals with autism spectrum disorder [13-20].



As is, the solution to many of today's challenges may be the leveraging of cutting-edge technologies to enhance autism intervention; these technologies include the use of machine learning, deep learning in artificial intelligence (AI), animated gaming, and data analytics. Computer-assisted interventions (CAIs) are particularly appealing to underresourced schools due to the potential to provide cost-effective individualized instruction and allow teachers to offer concurrent group instruction. Several available CAIs have integrated evidence-based interventions and complement current therapies for individuals with ASD [21].

Research suggests that CAIs, when applied effectively, can enhance learning by fostering four key components of the learning process: (1) active engagement, (2) group participation, (3) regular interaction and feedback, and (4) integration with real-life settings [22]. Furthermore, the convenient access of CAIs among parents and therapists allows ease of access to these technologies right in the palm of their hands [23]. During the recent COVID-19 pandemic, there was significant disruption and reduction in conventional therapies. As a means to continue therapy, many therapists sought to use CAIs, leading to a jump in usage from 15% to 61% [24].

Through the use of intelligent systems–based AI technologies, therapists and parents alike can provide supplementary and consistent therapy to individuals with ASD and enhance outcomes [25-28]. In 2 recent articles, the prospect of integrating AI into standard practices for autism therapy has great potential to improve social and communication outcomes in individuals with autism [29,30].

The integration of video modeling in ABA allows the individual to observe a recorded video of a specific task, gradually enabling independent performance by clearly presenting the instructions and essential stimuli needed to complete the task. Several studies have demonstrated the effectiveness of this strategy across various complex social tasks, such as acquiring conversational skills, commenting, complimenting, and enhancing pragmatic

abilities, as well as initiating and maintaining social relationships [31].

Gaming systems provide a sensory stimulus, where numerous studies have found an attraction factor for participation through a framework or application that provides additional animation and images [32,33]. AI-driven games can improve cognitive skills, social interaction, and emotional regulation. Such games can be modified to the specific needs of individuals with autism, offering personalized learning objectives. Studies have suggested that integrating AI-based interventions into standard therapy can improve the behavioral patterns of children with autism [34,35]. Animation games use engaging animated characters and scenarios to teach essential skills, making learning enjoyable and less stressful for children with autism, thus improving their attention span and resulting in a greater retention of learned skills. Studies using animation-based interventions have observed significant improvements in language acquisition and social skills [36,37]. All these technology-driven solutions have been shown to significantly enhance outcomes and bridge the limitations of therapists and parents in managing challenging behaviors among children with ASD.

As a result, CognitiveBotics, an AI-powered assistive technology, was designed and developed. The platform allows children with autism and their parents and therapists to effortlessly access its program anytime, anywhere, since it only requires a gadget (eg, a laptop or tablet) and access to an internet connection. The development process involved a multidisciplinary approach, combining insights from clinical psychology, child development, and technology experts. The platform provides a "digital" VARK (visual, auditory, read/write, and kinaesthetic) opportunity range to help children acquire social, communication, emotional, and behavioral skills, while automatically recording progress for therapists [38]. For parents, the platform is an easy-to-use digital tool offering training sessions on strategies and techniques, ensuring continuity of therapy at home. For further information on the platform, visit [39].

During the COVID-19 pandemic, a survey was conducted among therapists working with children diagnosed with ASD. Due to the reduction in conventional therapies, the therapists observed a moderate to severe impact on individuals' learning (73%), while parents were impacted emotionally and psychologically (85%). Before the pandemic, only 22% of therapists expressed a willingness to use any digital technology in autism intervention, however, this number tripled to 65% due to the constraints imposed by the lockdown [40]. There was an urgent need for standardizing digital health technologies that can be parent-mediated [41]. An initial pilot study was conducted between November 2020 and April 2021 to assess the software's capabilities using a set of 19 different skills. Throughout the study, the software effectively collected and recorded data during the user interaction, demonstrating its effectiveness in real-time data collecting and analysis [40].

Subsequently, to further evaluate the effectiveness of the CognitiveBotics AI-based platform in augmenting therapies for individuals with ASD, an observational, longitudinal study with an adequate sample size was conducted to assess different domains—the social/emotional, language/communication, and cognitive development of individuals who used the platform for 12 months. The initial study revealed minor glitches, which were promptly addressed, and parents of the individuals expressed a willingness to continue using the app, highlighting its potential impact.

Methods

Overview

The observational, longitudinal study was designed to evaluate the effectiveness of the CognitiveBotics AI-based software over a 12-month period. By understanding the practical challenges and assessing the software's effectiveness, the study provides a foundation for the future development and design of a trial.

The primary objectives of the study are as follows:

1. User engagement: assess the ability of both children and parents to effectively use the software and follow web-based instructions.
2. Progress tracking: evaluate the software's capability to automatically log the child's daily progress and provide visual graphical feedback on the dashboard.
3. Efficacy measurement: using established clinical parameters to evaluate progress at T1 and T2 across multiple measures.

Scoring Systems

Qualified therapists conducted assessments at baseline and at a 1-year follow-up, using the following specific parameters to evaluate progress over time.

The Childhood Autism Rating Scale (CARS) score is a factor analysis–based scale used for assessing the presence and severity of symptoms of autism spectrum disorders [42]. Scores between 30 and 37 are considered as mild to moderate autism and scores between 38 and 60 are considered as a severe level of autism. According to Russell et al [43], CARS has an acceptable level of sensitivity and specificity in Indian populations.

The Vineland Social Maturity Scale (VSMS) scores were compared between groups, assessing changes in social age (SA) and social quotient (SQ). This scale has been used to measure the adaptive behaviors of children with or without ASD by measuring their developmental profile in 8 domains and scoring SA and SQ. Originally developed by Doll in 1935 [44], VSMS was adapted by Malin in 1956 [45] to better suit the Indian population, ensuring its cultural relevance and applicability. This adaptation was further modified by Bharatraj in 1992, incorporating additional changes [46].

The Developmental Screening Test (DST), which measures developmental age (DA) and developmental quotient (DQ), assesses the developmental progress of children across various domains, including motor skills, language, social behavior, and cognitive abilities. It helps in determining the DA and DQ of the participants, which reflects their level of functioning in comparison to typical developmental milestones [47]. Recognizing that many developmental assessments at that time were standardized on Western populations, in 1977, Bharatraj adapted the DST to be more sensitive to the developmental norms of Indian children [48].

The Receptive and Expressive Emergent Language (REEL) test is designed to identify infants and toddlers who have language impairments or who have other disabilities that affect language development. It has 2 core subtests, receptive language age (RLA) and expressive language age (ELA), which are based on caregiver reports and converted into age-equivalent scores. A study conducted with Hindi-speaking children found the REEL assessment to be valid, reliable, and effective in assessing language outcomes [49].

Recruitment

Recruitment for the study took place from January to April 2023 and the completion of the study was 12 months after the last participant was recruited. Parents whose children were diagnosed with ASD and attending Rainbow Hospital in India were identified by the clinical team. Recognizing that individuals with ASD may have a higher chronological age but a lower social or developmental age, participants were accepted if their social or developmental age was between 2 and 18 years. The parent information sheet regarding the study was provided to all identified parents. Parents who expressed interest in their child's participation were contacted by the principal investigator's team. Textbox 1 shows the inclusion, exclusion, and withdrawal criteria of the study.

Textbox 1. Inclusion, exclusion, and withdrawal criteria for participants.

Inclusion criteria

Children who met all the following inclusion criteria were enrolled in the study:

1. Children diagnosed with autism spectrum disorder using assessment scales such as the Childhood Autism Rating Scale.
2. Children aged between 2 and 18 years.
3. Children with associated comorbidities were included on the condition that the child can use the platform.
4. Children with the ability to understand and respond to instructions given in English.
5. Children with access to a device on which the software can be accessed using an internet connection.
6. Children with parents who consented for their child to use the software.

Exclusion criteria

1. Children with parents who were not willing to consent to the study.
2. Children without access to a tablet, computer, or internet connection.
3. Children unable to understand English.

Withdrawal criteria (removal of participants from the therapy or assessment)

Any participant was allowed to voluntarily discontinue participation in the study at any time after giving informed consent and before the completion of the last visit of the study. This would not affect the care provided by their clinical team. The reasons for participant withdrawal were recorded and included but were not limited to the following:

1. Participant was no longer willing to continue in the study.
2. Study termination by sponsor or independent ethics committee.
3. Investigator's discretion (for safety reasons).

When a participant withdrew from the study, the investigator clearly documented the reason in the medical records and completed the appropriate case report form describing the reason for discontinuation. In addition, every effort was made to complete the appropriate assessment.

During this stage, the study objectives and procedures were thoroughly explained, and any questions from the parents were addressed. Informed consent was obtained from those who agreed to participate, and documentation was appropriately maintained. At baseline, clinical assessments including the CARS, DST, VSMS, and REELs were administered. Parent training sessions, conducted either online or offline, were arranged to familiarize parents with the platform and its usage. Parents who had training were granted access to the software and instructed to ensure their children used the software for at least 20 minutes per session, with a minimum of 3 sessions per day over 12 months, followed by home-based activities to reinforce learning. At the beginning of the study, we requested parents to use the software in addition to the standard care they were providing to their children and for ethical reasons did not ask them to stop any other treatments or therapies.

Participants were scheduled for 3 visits during the active study period:

- Visit 1 (day 0, T1): baseline clinical assessments were conducted.
- Visit 2 (6 months): clinical parameters were reassessed.
- Visit 3 (12 months, T2): final clinical assessments were conducted.
- Data from the software tracking the child's progress were collected for statistical analysis at each stage.

Additionally, a follow-up phone call was made every 15 days between the physical visits to verify the child's regular usage of the software and address any concerns. This telephonic follow-up ensured adherence to the study protocol and provided support for parents throughout the trial.

Software-Delivered Program

Using tablets or a computer, the platform offers evidence-based therapeutic interventions through a high-quality, patented software program that addresses a broad spectrum of learning difficulties by teaching small, key behaviors incrementally. This aims to improve learning outcomes and developmental progress in individuals with ASD by providing a comprehensive digital platform that supports various learning styles and therapeutic needs. It is designed to personalize learning, adjust difficulty levels, and provide real-time feedback and support to both parents and children.

Upon initially using the platform, parents were registered in the system and requested to complete an auto-generated individualized learning plan (ILP) questionnaire generated by the software. This enabled the software to ascertain the child's current developmental state and learning needs. If there were any difficulties or queries from the parents regarding the questionnaire, a study coordinator was available to assist with the onboarding process. Parents were then requested to attend a webinar session, where an interactive orientation on the software and its features was given, and any queries were addressed. Additionally, parents received a user manual and a navigation video for reference. Participation in this webinar session was mandatory before an ILP was assigned to the child.

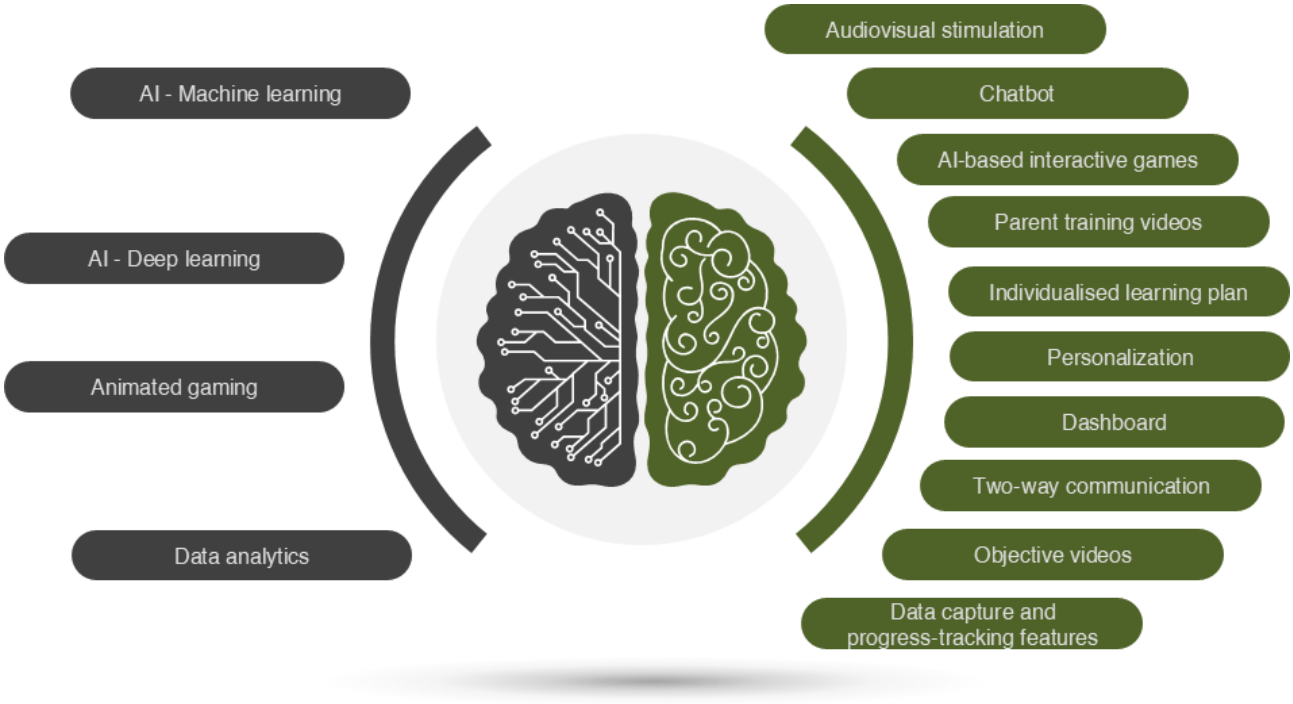
Based on the parental responses and child assessments, an ILP consisting of 3 target goals was generated by AI models focusing on 4 domains (social/emotional, language/communication, cognitive, and movement/physical development). Table 1 contains the lesson plan within the software and its advantages in providing adjunct therapy to children with ASD. The content is personalized and mapped to individual learning objectives, guided by therapist-defined developmental goals.

Table . Lesson plan structure and associated advantages of the platform.

Goal/skill domain	Task/learning objective	Methodology and advantages
Eye contact/attention	Looking at the object	Gamified, visually engaging content designed for children with neurodiverse profiles. Encourages sustained visual attention through interactive elements.
Eye contact/attention	Responding to name	Multimodal cues and visual prompts enhance auditory responsiveness and social awareness.
Imitation skills	Imitating arm, leg, or facial movements	Structured video models guide imitation in a low-anxiety, judgment-free digital space.
Cognitive skills	Number identification, shape recognition	Tasks scaffold foundational academic concepts in a playful, exploratory manner.
Communication/language	Labeling objects, requesting help	Activities promote expressive and receptive communication. Coviewing with caregivers enhances language modeling.

Before engaging in any lessons, parents were encouraged to watch the objective videos to improve the reasoning of mastering each goal. A practice session was available for skill reinforcement; however, the scores in these practice sessions were not recorded for progression to the next stage. Each daily practice session lasted 20 minutes, after which the software automatically concluded the learning session and redirected the child to the dashboard. If the caregiver determined that the child was prepared for an additional session, they had the option to initiate a new session., Overall, there are 227 activities or tasks organized under goals. Figure 2 presents the technologies and features of the CognitiveBotics platform.

Figure 2. The technologies and features in the software. AI: artificial intelligence.



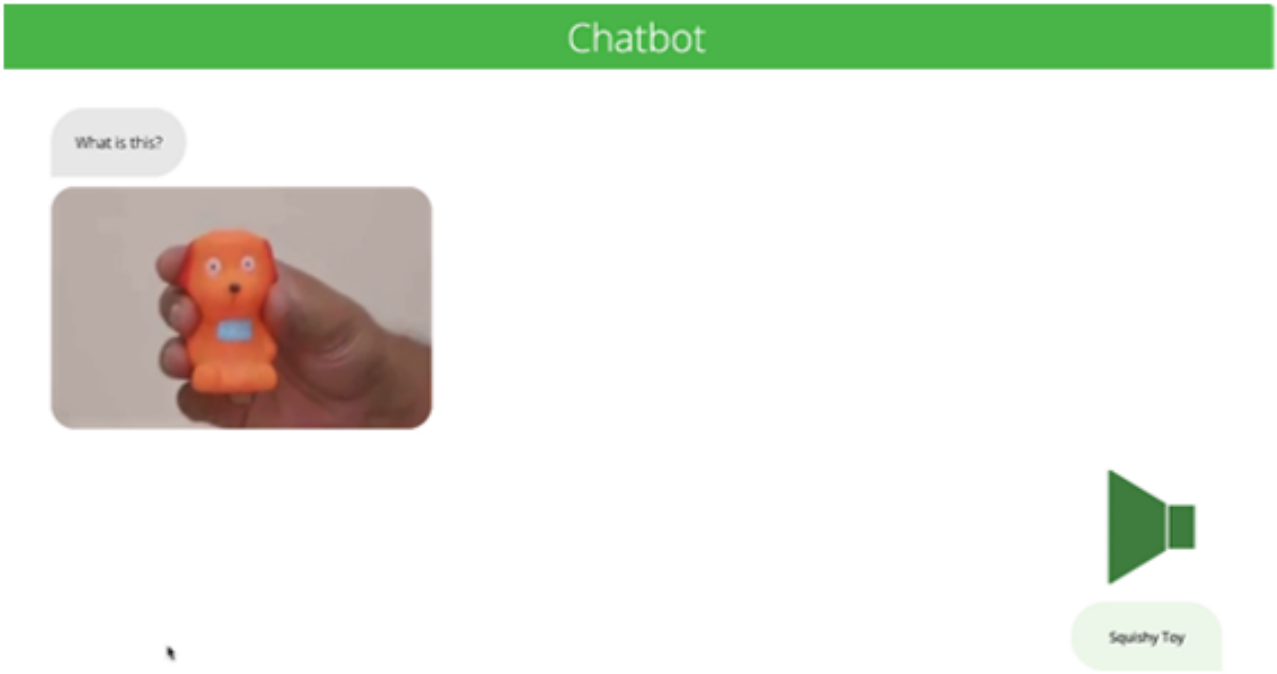
The session begins with the caregiver launching the daily schedule on the CognitiveBotics app. This schedule presents a sequence of personalized tasks aligned with the child's developmental goals. Each task is supported by engaging, gamified digital content designed specifically for children with ASD. Caregivers are encouraged to coview and participate in the learning process, fostering emotional bonding and reinforcing engagement through shared experience. Alternatively, under parent supervision, the child may explore the content independently, depending on their comfort and developmental level.

Once the child achieved 3 goals, a new ILP with a new set of 3 goals was created. To achieve each goal, the child is taught through 4 modalities:

- Audiovisual stimulation: Concepts are introduced through video modeling with interactive questions embedded within the content, increasing with complexity across four levels (level 0, 1, 2, and 3). Prompts are provided to guide the child's learning and are gradually reduced as the child becomes more proficient.
- Chatbot: This feature uses interactive questions to reinforce learning and promote generalization. The feature is particularly effective in fostering verbal engagement and enhancing the child's communication skills. An example of a chatbot goal is given in Figure 3.
- AI-based interactive games: Learning is facilitated through AI-driven interactive games that are tailored to each child's learning style, making the learning engaging and adaptive to individual needs.
- Home-based parent training videos: To support home-based activities, parents are provided with instructional videos that demonstrate how to apply the skills learned by their child in various settings, thus reinforcing learning outside the therapy center. The child's performance is assessed using 3 metrics captured by the software: first-time rights (accuracy of initial responses), correct questions (total number of correctly answered questions), and number of questions attempted (total engagement with the learning material). Once the lesson is mastered, the software automatically assigns the next set of goals.

If a child is not progressing toward their goals, the system proactively alerts the parents and therapists. Separately, parents are instructed to record a video of the lesson and submit it to the study coordinator or therapist team for review. In response, therapists will simplify the web-based goals to better suit the child's needs. Should the child continue to struggle, parents will receive a notification prompting them to resubmit the ILP checklist. Following this, the system will reassign 3 new goals, which will be carefully verified by therapists to ensure they align with the child's learning trajectory.

Figure 3. A screenshot of a lesson and an example transcript of a child-software interaction.



Software: *"Hi [Child's Name]! Let's name the object"*
(*[Object] appears on the screen...*)
Software: *[Child's name]!* What is this?
(Child should respond "Squishy toy"
(*If the child does not respond, the caregiver points at [object] on the screen*)
Software: *What is this?*
(*If the child still does not respond...*)
Software: *"Squishy Toy". [Child's Name] say "Squishy toy."*
(*If the child responds...*)
Software: *"Great job, [Child's Name]! Let's continue!"*
(*If the child did not respond...*)
Software: *"Great job, [Child's Name]!*
(Software moves on to the next goal and repeats this lesson the next day until the child masters the goal.

Other Core Features of the Platform

Other core features of the CognitiveBotics platform include the following:

- ILP progression: The software adjusts the level of difficulty of the ILP based on the child's progress, providing necessary assistance and notifications to parents and therapists.
- Personalization: Personalization is a unique feature, where all learning goals are delivered in a personalized and customized manner, tailored to the specific needs of each child. During interactive sessions, the system personalizes by using the child's name while asking the interactive questions, drawing the child's attention.
- Dashboard: A daily progress graph is displayed on the child's dashboard, which is accessible to both parents and therapists, offering real-time insights into the child's development.
- Two-way communication: The software includes a fun activity that detects and encourages body part interactions, in addition to occupational therapy tasks, promoting overall development from a young age.
- Objective videos: Parents are empowered through videos that outline the objectives of each task, enabling them to actively participate in and support their child's learning.
- Data capture and progress tracking features: Aim to automate monitoring and capture the child's progress based on key learning principles—attention, retention, and

generalization, such as “eye gaze detection.” These data are presented in a user-friendly format on a dashboard, facilitating easy comprehension for both parents and therapists.

Fidelity of Implementation Data

The fidelity of implementation was assessed via a multitiered approach to ensure attendance to the session lessons. The software has an automated session notification and progress tracker to prompt parents to complete assigned goals within the learning plan. To progress to the next learning level, mandatory successive mastering of goals is required. This ensures that all lesson components were completed as intended. Additionally, therapist-led monitoring and follow-up calls were conducted to monitor progress, reinforce engagement with the intervention, and address any caregiver-reported concerns to ensure fidelity.

Caregivers underwent a structured training program on reinforcement strategies aimed at ensuring consistency in their interactions with the child beyond software-guided sessions. This training equipped caregivers with evidence-based behavioral techniques that align with the principles of ABA and developmental learning models, such as immediate reinforcement or reward systems. Furthermore, to encourage parental involvement, caregivers were provided zero-fee in-person therapy sessions at the center, on the condition their child is actively engaged with the platform.

Lastly, software usage was collected at the back end, tracking metrics such as log-in frequency, time spent on lessons, and completion rates. This allowed the software programmer to evaluate the platform utilization and adherence. Any deviations from the lesson plans were brought to the attention of the therapist. Together, these mechanisms ensured consistent implementation and provided opportunities for timely intervention when necessary.

Statistical Analysis

After completion of the study, the data were analyzed to compare the effectiveness of the CognitiveBotics platform between the intervention and control groups. For each group and clinical assessment parameter, the mean scores and standard deviations were calculated at 2 stages: the start of the study (T1) and the end of the study (T2). The mean change and percentage mean change from T1 to T2 were also computed. To determine the statistical differences, the *P* values were calculated using the Mann-Whitney *U* test, with a *P* value of <.05 being considered as statistically significant.

Ethical Considerations

This study was conducted in accordance with the study protocol, the New Drugs and Clinical Trials Rules 2019 issued by the Government of India, the ethical principles that have their origin in the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013), the International Council for Harmonisation Good Clinical Practice, and all applicable local regulatory requirements. The investigators agreed to conduct the study according to the principles of the International Council for Harmonisation Good Clinical Practice, as well as in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the protocol, and all national, state, and local laws or regulations. The medical care given to and medical decisions made on behalf of study participants were always the responsibility of a principal (site) investigator. Each individual involved in conducting the study was qualified by education, training, and experience to perform his or her respective task(s).

Informed consent was obtained from the parents or legal guardians of all participants. The study details were thoroughly explained, including the study’s purpose and procedures and the voluntary nature of participation. Parents were informed that they and their children were free to withdraw from the study at any time, with no impact on their routine activities or any other services received. As this study included human participants, the collection of data from medical records, as well as software usage, it adheres to all institutional ethical guidelines. Ethical approval for this observational study was obtained from the Institutional Ethics Committee of the Rainbow Children’s Medicare (registration number EC/RENEW/INST/2021/10510).

Before any collection of data, the study protocol, participant information sheets, and informed consent forms were reviewed and approved. The data were maintained throughout the study, with all reports and communications relating to participants being kept confidential. Names and other identifiable details were removed, and all records were coded using unique identification acronyms. No images or video recordings of participants are included in the manuscript. No monetary compensation was provided to the participants or their families. However, participants in both the intervention and control groups received free access to the software platform, as well compensation for travel expenses when coming to the center for assessments.

Results

Participant Selection and Characteristics

The results of this study examine the impact and utility of the CognitiveBotics platform for children with ASD over a 12-month observational period. Key outcomes focus on quantitative measures of behavioral, developmental, and language-based parameters. An intervention versus control analysis was performed, organized by baseline (T1) and end-of-study (T2), to ascertain the software’s impact across multiple functional and developmental domains, namely CARS, VSMS, DST, and REEL scores. This approach provided structured insights into the software’s influence on each parameter and allowed for comparative analysis of outcomes over time.

Figure 4 illustrates the study’s recruitment and retention flow. Of an initial total of 88 enrolled participants, 43 completed the study, while 35 continued to use the software for the entire 1-year duration, and 5 did not use the software but participated in the 1-year follow-up assessments, and were categorized as the control group. A further 3 participants were labeled as outliers and were excluded from further analysis. Table 2 shows

the key baseline demographic characteristics of the 40 participants who completed the study.

Figure 4. Flowchart of participants in the study.

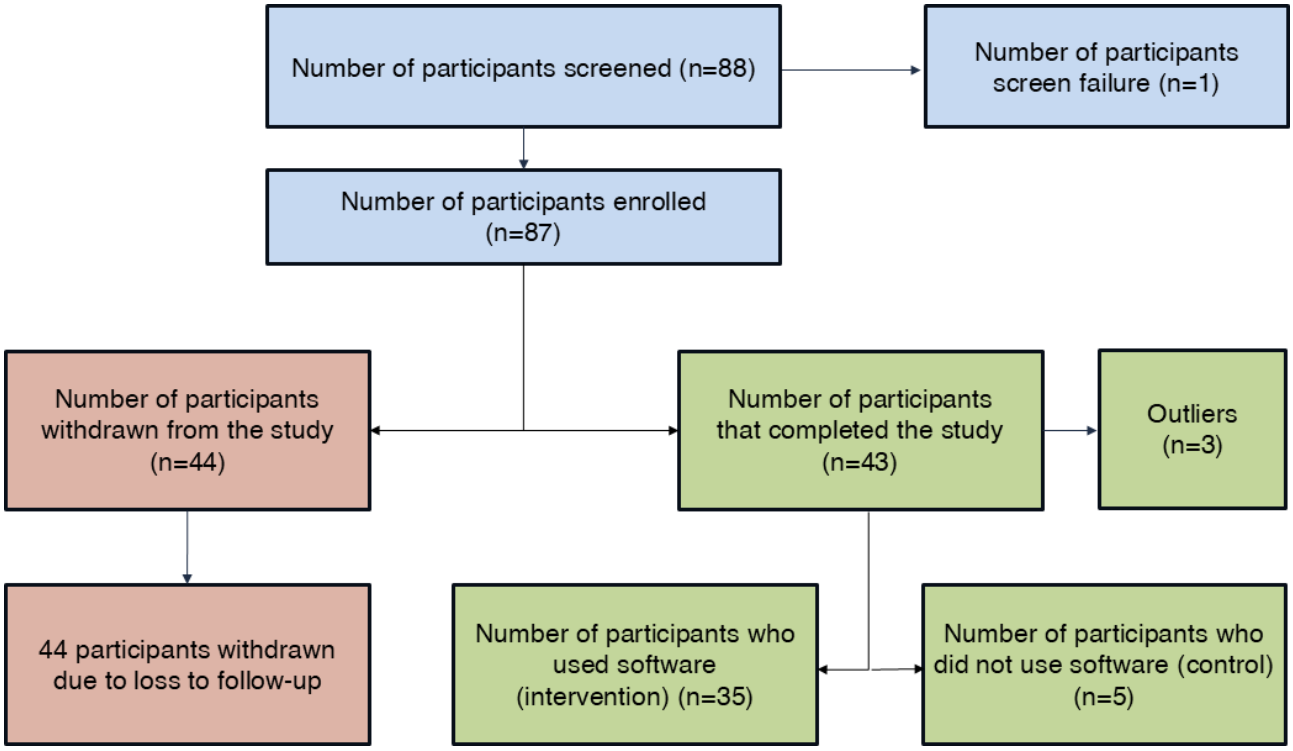


Table . Comparison of baseline demographics of participants in the intervention and control groups.

Parameter and statistics		Intervention (n=35)	Control (n=5)	Overall (n=40)
Age (years)				
	Mean (SD)	43.71 (SD 15.48)	44.60 (SD 14.98)	43.83 (SD 15.23)
	Median	39.00	39.00	39.00
	Quantile	31.50; 52.00	33.00; 54.00	31.75; 54.50
	Range	25.00 - 87.00	31.00 - 66.00	25.00 - 87.00
Gender, n (%)				
	Male	33 (94)	3 (60)	36 (90)
	Female	2 (6)	2 (40)	4 (10)

The participants in the intervention group were stratified into 3 developmental groups based on chronological age:

- Toddler group (n=12): children aged 2 - 3 years
- Preschool group (n=15): children aged 4 - 6 years
- School-aged group (n=8): children aged 7 - 8 years

The purpose was to assess the impact of the intervention across different developmental ages, considering variations in cognitive, language, and social skills.

Based on the study location, the majority of participants were of South Indian descent and from families with a higher educational background. All participants showed delays across multiple developmental domains, necessitating structured therapeutic intervention. Their academic skill levels in reading, writing, and mathematics were rudimentary, with significant challenges observed in social/emotional, language/communication, cognitive, and movement/physical development.

Intervention and Control Group–Based Analysis Using Different Parameters

The study evaluated outcome measures in the intervention and control groups across T1 (baseline) and T2 (12 months), assessing CARS, SA, SQ, DA, DQ, and REEL scores.

Table 3 shows the outcome measures of 35 participants in the intervention group, which were compared across T1 and T2. For the CARS score, there was a significant decrease from 33.41 (SD 1.89) at T1 to 28.34 (SD 3.80) at T2, showing a mean change of 5.07 and a percentage change of 15.18% (P<.001).

Table . Comparison of outcome measures in the intervention group only at baseline (T1) and end of study (T2).

Parameters	Intervention group (n=35)				
	T1[a], mean (SD)	T2[b], mean (SD)	Mean change	Mean change, %	*P* value[c]
CARS[d]	33.41 (1.89)	28.34 (3.80)	5.07	15.18	<.001
SA[e]	22.80 (7.33)	35.76 (9.09)	12.96	56.84	<.001
SQ[f]	53.26 (11.84)	64.75 (16.12)	11.49	21.57	<.001
DA[g]	30.93 (9.91)	45.31 (11.20)	14.38	46.49	<.001
DQ[h]	70.94 (10.95)	81.33 (16.85)	10.39	14.65	<.001
RLA[i]	22.09 (8.94)	34.51 (14.93)	12.42	56.22	<.001
ELA[j]	18.69 (8.52)	29.89 (15.60)	11.20	59.93	<.001

[a]T1: start of the study.

[b]T2: end of the study.

[c]*P* value was calculated using the Mann-Whitney *U* test.

[d]CARS: Childhood Autism Rating Scale.

[e]SA: social age.

[f]SQ: social quotient.

[g]DA: developmental age.

[h]DQ: developmental quotient.

[i]RLA: receptive language age.

[j]ELA: expressive language age.

In the SA score, there was a significant improvement from 22.80 (SD 7.33) at T1 to 35.76 (SD 9.09) at T2, with a mean change of 12.96 and a percentage change of 56.84% (*P*<.001).

In the SQ score, there was an improvement from 53.26 (SD 11.84) at T1 to 64.75 (SD 16.12) at T2, with a mean change of 11.49 and a percentage change of 21.57% (*P*<.001).

In the DA score, there was an improvement from 30.93 (SD 9.91) at T1 to 45.31 (SD 11.20) at T2, showing a mean change of 14.38 and a percentage change of 46.49% (*P*<.001).

In the DQ score, there was an improvement from 70.94 (SD 10.95) at T1 to 81.33 (SD 16.85) at T2, showing a mean change of 10.39 and a percentage change of 14.65% (*P*<.001).

In the REEL score, the RLA showed a substantial increase from 22.09 (SD 8.94) at T1 to 34.51 (SD 14.93) at T2, with a mean change of 12.42 and a percentage change of 56.22% (*P*<.001). Similarly, the ELA exhibited a significant increase from 18.69 (SD 8.52) to 29.89 (SD 15.60), showing a mean change of 11.20 and a percentage change of 59.93% (*P*<.001).

Table 4 shows the outcome measures of 5 participants in the control group, which were compared across T1 and T2. For the CARS score, there was a significant decrease from 33.90 (SD 1.24) at T1 to 30.30 (SD 3.68) at T2, showing a mean change of 3.6 and a percentage change of 10.62% (*P*=.06).

Table . Comparison of outcome measures in the control group only at baseline (T1) and end of study (T2).

Parameters	Control group (n=5)				
	T1[a], mean (SD)	T2[b], mean (SD)	Mean change	Mean change, %	*P* value[c]
CARS[d]	33.90 (1.24)	30.30 (3.68)	3.6	10.62	.06
SA[e]	21.41 (5.44)	32.60 (8.24)	11.19	52.27	.06
SQ[f]	49.13 (5.45)	58.77 (14.73)	9.64	19.62	.12
DA[g]	28.30 (6.69)	41.00 (7.04)	12.7	44.88	.06
DQ[h]	65.60 (11.68)	72.97 (7.22)	7.37	11.23	.19
RLA[i]	19.60 (7.13)	26.40 (9.53)	6.80	34.69	.10
ELA[j]	16.80 (4.60)	23.60 (6.23)	6.80	40.48	.054

[a]T1: start of the study.

[b]T2: end of the study.

[c]*P* value is calculated using Mann-Whitney *U* test.

[d]CARS: Childhood Autism Rating Scale.

[e]SA: social age.

[f]SQ: social quotient.

[g]DA: developmental age.

[h]DQ: developmental quotient.

[i]RLA: receptive language age.

[j]ELA: expressive language age.

In the SA score, there was a significant improvement from 21.41 (SD 5.44) at T1 to 32.60 (SD 8.24) at T2, with a mean change of 11.19 and a percentage change of 52.27% (*P*=.06).

In the SQ score, there was an improvement from 49.13 (SD 5.45) at T1 to 58.77 (SD 14.73) at T2, with a mean change of 9.64 and a percentage change of 19.62% (*P*=.12).

Similarly, in the DA score, there was an improvement from 28.30 (SD 6.69) at T1 to 41.00 (SD 7.04) at T2, showing a mean change of 12.7 and a percentage change of 44.88% (*P*=.06).

In the DQ score, there was an improvement from 65.60 (SD 11.68) at T1 to 72.97 (SD 7.22) at T2, showing a mean change of 7.37 and a percentage change of 11.23% (*P*=.19).

In the REEL score, the RLA showed a substantial increase from 19.60 (SD 7.13) at T1 to 26.40 (SD 9.53) at T2, with a mean change of 6.80 and a percentage change of 34.69% (*P*=.10). The ELA exhibited an increase from 16.80 (SD 4.60) to 23.60 (SD 6.23), showing a mean change of 6.80 and a percentage change of 40.48% (*P*=.054).

Overall, the intervention group presented substantial improvements across all outcome measures, particularly in CARS, SA, and language scores (RLA and ELA), with the majority of these changes reaching statistical significance. This indicates that the platform may enhance social, cognitive, and language outcomes in the intervention group. In contrast, the control group of 5 participants showed positive changes but with less significance and the changes were statistically weaker across measures.

Discussion

Principal Findings

This study demonstrated that CognitiveBotics, an AI-powered assistive technology, has made significant gains in developmental and social parameters over the course of 12 months in children diagnosed with autism. Both parents and therapists have reported minimal negative behavioral changes while using the platform, including screen addiction and sleep disturbances. In intervention versus control analysis, there were significant improvements in the intervention group, particularly in those with higher baseline levels of functioning, underlining the efficacy of the software in reducing autism severity and enhancing developmental skills in children with ASD. Accompanied by highly significant *P* values, the intervention group showed an improvement in symptoms, as well as marked enhancements in social skills, developmental age, and language abilities.

The CognitiveBotics software, like many other available ABA-assistive technologies, was observed to have various benefits and advantages specifically for individuals with ASD [50]. Supported in laptops and tablets, the platform is commonly available, affordable, and socially acceptable, making it an ideal tool for parent-mediated interventions [51,52]. Using the platform, parents played a crucial role in supporting their children's learning, observing better improvements compared to the control group using only traditional therapy. The software helps enhance attention span and motivation during learning activities, offering engaging, interactive experiences that increase children's participation [53,54].

Within a learning environment, the software increases interaction and participation and improves the learning process [55]. Additionally, the software provides real-time feedback on key skills and is customizable to focus on individual needs, similar to the benefits seen in the Picture Exchange Communication System and other visual aids, texts, and sounds [56,57]. The portability of the devices can allow parents to provide learning at times when the child is most receptive, despite the unavailability of therapists. Furthermore, parent-implemented technologies can be the most readily and affordably deployed, and such assistive technology enables parents to offer the most opportunities for social contact [58]. The software incorporates interactive games that improve social-emotional functioning and behavior. The interactive feature allowed the participants to recognize emotions, use deconfliction strategies, collaborate with others, and address issues like greeting known people like teachers or neighbors. In a recent study, parents who used social skills programs incorporating features similar to those in the CognitiveBotics platform found significant improvements in social skills and reductions in problematic behaviors, in contrast to those in the control group [59].

There may be certain shortfalls with the use of ABA assistive technologies, but as with any problem, there are solutions that can overcome such shortfalls. The first area of concern is increased screen time, possibly leading to restricted or repetitive behaviors, lack of socializing, and concerns over metabolic and sleep disturbances [60,61]. In such circumstances, CognitiveBotics has incorporated a preset screen time feature of 20 minutes, after which the session concludes and takes the user to the dashboard. It is also advisable to provide minimal access in a group setting to reduce potential isolation [62]. Devices may also be misused to view passive content, in which case supervised coviewing with parents is advised [63]. Furthermore, the choice of content has to be predetermined, whereby highly interactive and engaging media is most beneficial to the child as it promotes engagement, motivation, and learning outcomes [64]. Another issue is the potential for tantrums if the device is removed. As is the case in other situations, when access to preferred items is interrupted, parents and therapists should be trained to control such behaviors.

In recent years, there have been numerous studies on the proposed use of tablets or computers in autism interventions. A meta-analysis conducted by Sandbank et al [65], reviewed 252 separate trials examining the efficacy of technology in autism interventions. The findings suggest an overall improvement in social communication skills and reductions in difficult behaviors, particularly when used by parents. This aligns with the intentions behind the CognitiveBotics platform, which aims to support individuals with autism and their families. Furthermore, a low incidence of adverse events reported when using such interventions supports adoption of the software in both home and clinical settings.

Novack et al [66] conducted a study to assess the effectiveness of mobile apps on the principles of ABA, particularly in assessing the impact on the receptive language skills of individuals. Randomized into an immediate-treatment or a delayed-treatment control group, the results indicated significant improvements in receptive language skills in the former group. However, the study had limitations, particularly with the absence of psychometric parameters to assess outcomes. Although improvements in receptive language skills were observed, the study is incomplete. Our 12-month study demonstrated how CognitiveBotics leverages AI to improve receptive language skills, offering prolonged benefits using personalized ABA-based interventions and addressing limitations in traditional psychometric assessments. Another study aimed at addressing social engagement by using a proposed 3D complex facial expression recognition system to recognize facial emotions; it found that, in 3 weeks, users had a marked improvement in identifying facial cues compared with the control group, with surprise and shy expressions being the easiest to identify [67]. Similarly, CognitiveBotics contains activities that enable children to better recognize and respond to social and emotional cues, significantly boosting their social communication skills within a short intervention period.

A study conducted in Saudi Arabia assessed the effectiveness of AI-driven apps in a traditional education setup. Apps such as “My School” and “Alfaz” were chosen for their adaptive and interactive content that aligned with the academic curriculum. Participants who received 60-minute sessions twice weekly for 5 weeks showed significant improvements in reading and math skills compared to those in the control group [68]. Similarly, our software incorporates real-time feedback, task adaptation, and data-driven insights to ensure that children receive targeted, engaging, and effective support, ultimately enhancing their cognitive and functional independence.

Lastly, a meta-analysis conducted by Moon et al [23] aimed to review the effectiveness of mobile apps in the treatment of individuals with ASD. After a review of 1100 randomized controlled trials, only 7 studies were deemed suitable for further analysis, suggesting a very methodological approach. Using the Mullen Scales of Early Learning, the results favored the intervention group, indicating a significant improvement in the participants’ early learning and developmental outcomes compared to control groups. Moreover, the analysis found minimal heterogeneity (P>.10) across different studies or no significant evidence of publication bias. Correspondingly, our platform aligns with these findings by offering a technology-based, interactive tool specifically designed to enhance learning and developmental progress in individuals with autism. With an emphasis on providing individualized interventions that target key skills, CognitiveBotics uses validated clinical parameters to monitor improvements, reducing inaccuracies, similar to the studies highlighted in Moon’s analysis [23].

Limitations of the Study

Although evidence from our longitudinal study shows significant improvement in outcome measures for individuals with ASD using the software, a few limitations have to be discussed. First, the small sample size of 40 participants is a critical limitation, suggesting inadequate generalization of the findings. However, most studies regarding children with autism often face challenges in recruiting adequate numbers of participants. Limited research has explored effective strategies for efficiently

recruiting participants with ASD, a challenge that poses a barrier to larger and more comprehensive studies in this field [69].

Second, the participants were recruited from a single center and predominantly came from literate and urban families. Such a demographic is not representative of the entire population of individuals with ASD, particularly in India. The benefits observed in using the software may not translate to individuals with a lower socioeconomic status or those located in rural areas, who may face different challenges and have different needs. Further studies should be conducted to include participants from rural areas and various socioeconomic backgrounds. This includes incorporating features that reflect local languages and cultural sensitivities to ensure the software is relevant and effective for a wider range of users.

Third, the study experienced a 59% attrition rate, which could be attributed to several factors, including language barriers or the demanding schedules of caregivers, which may have limited their ability to fully engage with the platform. Such high levels of attrition are commonly observed in digital therapeutics for mental health. Similarly, a recent meta-analysis found more than half of the users discontinued using smartphone apps aimed at treating depressive symptoms [70].

Finally, while randomized controlled trials are considered the gold standard for assessing the effectiveness of interventions, their feasibility in such a population remains challenging. To address this, future research should explore methodologies that balance scientific rigor with practical implementation to further validate the software's effectiveness among different subgroups.

Conclusions

This 12-month study demonstrated that the CognitiveBotics platform delivering parent-mediated interventions significantly improved multiple developmental and social parameters in participants. Furthermore, it highlights that these digital technologies using audiovisuals, AI-based interactive games, animation games, and chatbots have an attraction factor that keeps the interest of children with ASD. Particularly, the incorporation of AI into digital technology has been shown to enhance social communication skills, especially in younger participants with learning difficulties, helping them reach their specific learning objectives.

Most assistive technologies are not intended to satisfy the needs of individuals with ASD as a whole, as they have variable needs. Despite being in its infancy, such digital technologies have been proposed to address the wide array of learning needs and work on the core symptoms of ASD. Further research must be conducted to include a larger number of children with different levels of social and developmental delays and ASD severity along with regional, linguistic, and sociocultural variations.

In conclusion, the promising results of this study underscore the potential of AI software interventions in revolutionizing holistic support for children with ASD. As these technologies continue to evolve, aligning the software not just to the needs of the child but also to those of parents and therapists offers hope for more personalized and effective strategies for not just children on the autism spectrum but also all neurodiverse children.

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Conflicts of Interest

The primary author (HA) is on the Advisory Board of CognitiveBotics. HA was also actively involved in designing the study methodology and contributed to drafting and revising the manuscript. The principal investigator (SN) conducted research at the study site and received an honorarium for overseeing the study's execution. The corresponding author (BRR) is currently employed at CognitiveBotics Technologies Private Limited.

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Abbreviations

ABA: applied behavioral analysis
AI: artificial intelligence
ASD: autism spectrum disorder
CAI: computer-assisted interventions
CARS: Childhood Autism Rating Scale
DA: developmental age
DQ: developmental quotient
DST: Developmental Screening Test
ELA: expressive language age
ILP: individualized learning plan
REEL: Receptive and Expressive Emergent Language Test
RLA: receptive language age
SA: social age
SQ: social quotient
VSMS: Vineland Social Maturity Scale

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Reduction of Anxiety-Related Symptoms Using Low-Intensity Ultrasound Neuromodulation on the Auricular Branch of the Vagus Nerve: Preliminary Study

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Abstract

Background: Neuromodulation of the auricular branch of the vagus nerve using low-intensity focused ultrasound (LIFU) is an emerging mode of treatment for anxiety that could provide a complementary or alternative treatment modality for individuals who are refractory to conventional interventions. The proposed benefits of this technology have been largely unexamined with clinical populations. Further research is required to understand its clinical potential and use in improving and managing moderate to severe symptoms.

Objectives: The aim of this study was to do a preliminary investigation into the efficacy, safety, and usability of the wearable headset that delivers LIFU to the auricular branch of the vagus nerve for the purpose of alleviating anxiety disorder symptoms.

Methods: This study was a pre-post intervention study design for which we recruited 28 participants with a Beck Anxiety Inventory score of 16 points or greater. Participants completed 5 minutes of treatment daily consisting of LIFU neuromodulation delivered to the auricular branch of the vagus nerve. Participants did this for a period of 4 weeks. Assessments of anxiety symptom severity (Beck Anxiety Inventory), depression symptom severity (Beck Depression Inventory), posttraumatic stress disorder symptom severity (Post Traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]), and sleep quality (Pittsburgh Sleep Quality Index) were taken prior to starting treatment and weekly for 4 weeks of treatment. Usability and safety were also assessed using an exit questionnaire and adverse event logging.

Results: After completing 4 weeks of LIFU neuromodulation to the auricular branch of the vagus nerve, the average Beck Anxiety Inventory score decreased by 14.9 (SD 10.6) points (Cohen d=1.06; P<.001), the average Beck Depression Inventory score decreased by 10.3 (SD 7.8) points (Cohen d=0.81; P<.001), the average Post Traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) score decreased by 20.0 (SD 20.5) points (Cohen d=0.94; P<.001), and the average Pittsburgh Sleep Quality Index score decreased by 2.2 (SD 3.1) points (Cohen d=0.65; P=.001). On the exit questionnaire, participants rated the treatment highly for ease of use, effectiveness, and worthiness of the time invested. Only 1 adverse event was reported throughout the entire trial, which was mild and temporary.

Conclusions: This preliminary study provided justification for further research into the efficacy, safety, and feasibility of using LIFU to modulate the auricular branch of the vagus nerve and reduce the symptoms of anxiety, depression, and posttraumatic stress disorder.

Trial Registration: ClinicalTrials.gov NCT06574971; https://clinicaltrials.gov/study/NCT06574971

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KEYWORDS

low-intensity focused ultrasound; auricular branch of the vagus nerve; anxiety; depression; posttraumatic stress disorder

Introduction

Anxiety is the “anticipation of real or imagined future threat or danger” [1], which manifests itself with a mix of emotional signals, such as hyperarousal and panic, and physiological ones, including increased heart rate, shortness of breath, sweating, and chest pain [2]. The emotional and physiological responses experienced with anxiety result from the activation of the hypothalamus, which engages the sympathetic nervous system (SNS) [3,4]. This sympathetic activation is adaptive in short bursts and enables us to handle threats and stressors, but in anxiety disorders, the SNS may be overly sensitive or chronically activated, leading to distress and health challenges over time [5,6]. Clinically significant anxiety symptoms are disproportionate to the future threat, endure after it has passed, and cause substantial distress or incapacitation [1,7]. The etiology of anxiety disorders is complex, with heritability ranging from 30% to 67% depending on the research study and

anxiety disorder type [1]. However, trauma, chronic stress, and other environmental factors play an important role in the development of maladaptive anxiety [7].

The complex etiology of anxiety opens opportunities for intervention at multiple points in the course of the illness from a variety of disciplines. There are also several multidisciplinary approaches that offer a more holistic care plan. The primary goal of preventative strategies is to lower the risk of developing disordered anxiety responses prior to onset. Preventative psychoeducational interventions for adolescents and adults have been shown to reduce the risk of anxiety onset [8] with small to moderate effect sizes [1,8]; however, studies of these interventions tend to end their follow-ups after only 9 months, so the long-term stability of their benefits after intervention completion is still in question [1]. Once an active anxiety disorder has developed, psychotherapeutic treatments for it range in intensity from self-guided programs to highly intense weekly sessions with a licensed therapist. Self-guided treatments derived from evidence-based psychotherapies are more effective than active controls but show smaller effect sizes than therapist-guided programs [9]. Cognitive behavioral therapy is widely considered to be the gold standard for anxiety disorder treatment, particularly in adults, although Haller et al [10] found mindfulness-based cognitive therapy and acceptance and commitment therapy to be similar in efficacy. In recent years, virtual psychotherapy modalities have emerged as a compromise that balances the convenience of self-help approaches and the rigor and guidance of a traditional in-person therapy session. Thus, recent advances in telehealth have paved the way for approaches that afford convenience and accessibility without a loss of efficacy [11,12].

Pharmacotherapy is similar in efficacy to psychotherapy, and both pharmacotherapy and psychotherapy are considered first-line treatments for anxiety disorders in most standard care plans [1]. Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, benzodiazepines, antipsychotics, and β-blockers are all used to treat anxiety. Despite this wealth of options, anxiety disorders remain chronic and refractory to treatment in many individuals, with 15% - 40% achieving less than 50% remission in symptoms [13]. Studies of combinations of psychotherapeutic and pharmacological approaches to anxiety treatment are sparse, leaving confusion surrounding which combinations are most efficacious [1]. Taken as a whole, while current neurobiological and psychosocial treatment approaches to anxiety disorders are sufficient for a large portion of affected individuals, there is still a substantial proportion of patients who would benefit from additional treatment options.

Low-intensity focused ultrasound (LIFU) is an emerging mode of treatment for anxiety that could provide an alternative treatment modality. LIFU can stimulate or inhibit neural activity, depending on the parameters of the energy applied to neural tissue. Also referred to as acoustic neuromodulation, the use of LIFU to modulate the activity of neural structures is a promising method for noninvasive treatment of neurological disorders [14]. While the majority of investigations featuring LIFU neuromodulation have primarily focused on modulation of neural structures within the central nervous system, disorders affecting the peripheral nervous system stand to benefit from this powerful tool as well [15]. LIFU neuromodulation of the peripheral nervous system is accomplished through a nonthermal, noncavitation bioeffect produced by setting the parameters to the intermediate intensity range. At intensities between 1 and 200 W/cm^2, ultrasound is able to noninvasively and reversibly enhance peripheral neural activities by activating low-threshold mechanosensitive nerve endings, opening mechanosensitive ion channels to evoke action potentials [15]. Ultrasound of intermediate intensity also enhances the neural activity of peripheral nerve axons, leading to increased nerve conduction velocities in both A- and C-type fibers, which is likely caused by mechanical gating of other ion channels [16]. In addition, enhanced neural activity could be attributed to a direct effect of acoustic radiation forces on the lipid-bilayer neural membrane. Plausible mechanisms for this include a transient capacitive current from rapid changes of local membrane capacitance and transmembrane pore formation to allow sodium and potassium ions to pass through [15,16].

The vagus nerve, also known as cranial nerve X, is the longest cranial nerve and its branches enable the organs to adjust to the demands of a person's internal state and external environment. The vagus nerve is a primary component of the parasympathetic nervous system, which, paired with the SNS, constitutes the autonomic nervous system [4,17]. Normally, sympathetic and parasympathetic nerve pathways act synergistically to create a state of equilibrium appropriate to meet the demands of the current internal state and external challenges. Disruption of the balance of sympathetic and parasympathetic activity in favor of sympathetic activity is one indicator of anxiety disorders [4,18].

The many branches of the vagus nerve are increasingly seen as pathways for promoting or restoring health and ameliorating the physiologic unease that gives rise to anxiety and other negative mental states [19]. The vagus nerve operates bidirectionally, meaning states of homeostasis and calm can be induced from the bottom up or the top down. The brain can use cognitive strategies to dissipate states of bodily unease (top down) or activate vagal nerve pathways to create psychological comfort and a sense of safety (bottom up) [20]. In addition to its role in regulating the parasympathetic nervous system, the vagus nerve also projects to the amygdala and hippocampus, both of which are important to extinction learning techniques commonly used in the treatment of anxiety and posttraumatic stress disorder (PTSD) [21,22]. Stimulation of the vagus nerve can downregulate sympathetic activity, restoring visceral order and psychological calm [23,24].

Early research into the clinical applications of vagus nerve stimulation (VNS) primarily centered on epilepsy and depression [17], but the vagus nerve is an attractive target for antianxiety therapies as well. In addition to its role in regulating the parasympathetic nervous system, the vagus nerve also projects to the amygdala and hippocampus, both of which are important to extinction learning techniques commonly used in the treatment of anxiety and PTSD [21,22]. Preliminary clinical studies have demonstrated VNS's therapeutic applications to treatment-resistant anxiety disorders [23] and long COVID-19

symptoms [25]. Physiological changes as an effect of VNS are also well known in the literature. Wittbrodt et al [26] discovered that transcutaneous cervical VNS increased activation of the anterior cingulate and hippocampus during exposure to traumatic scripts. Lamb et al [27] found that transcutaneous auricular vagal nerve stimulation (taVNS) improved respiratory sinus arrhythmia and skin conductance during exposure to physical and emotional stress. Bremner et al [28] found that transcutaneous cervical VNS decreased inflammatory markers and sympathetic tone while increasing medial prefrontal function during exposure to trauma-specific and neutral stressors.

While VNS is traditionally done electrically, ultrasound's noninvasiveness and specificity make it ideal for VNS [29]. Ultrasound has been successfully used for vagus nerve neuromodulation in rats [30] and for peripheral nerve [29] and suborgan [31] stimulation in humans. With a recent study showing the feasibility of transauricular VNS as an at-home intervention [20,22], transauricular ultrasound VNS has emerged as a noninvasive, yet potentially effective, at-home treatment for the management of anxiety symptoms. In response to this, we have developed a wearable headset with an ultrasound transducer that delivers LIFU to the auricular branch of the vagus nerve that can be used at home for treatment of anxiety symptoms. The purpose of this study was to do a preliminary investigation into the efficacy, safety, and usability of the wearable headset that delivers LIFU to the auricular branch of the vagus nerve for the purpose of alleviating the symptoms of anxiety. Because depression [32] and PTSD [33] frequently co-occur with anxiety, we also investigated the efficacy of transauricular ultrasound VNS for alleviating the symptoms of depression and PTSD in individuals with anxiety.

Methods

Study Design

This was a pre-post-intervention study in which all participants received the intervention daily, at home, for a period of 4 weeks. The clinical trial is registered at ClinicalTrials.gov [NCT06574971]. Informed consent was obtained from each of the 28 participants prior to screening. All activities were completed remotely and a ZenBud device with a user manual and participant instructions was shipped to each participant's home. Participants completed 5 minutes of LIFU to the auricular branch of the vagus nerve each day using the ZenBud device. Treatment could be completed at any convenient time of day and did not have to be completed at the same time every day, as long as the treatment was completed within every 24-hour period. Assessments were completed on the web on the day before the first treatment session and then weekly. The final assessment was completed on the day of the final treatment after the final treatment session. The battery of assessments included 4 validated clinical outcome measures: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), PTSD Checklist for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-V*) (PC5), and Pittsburgh Sleep Quality Index (PSQI). The details of these assessments are further described in the data collection section.

Participant Recruitment

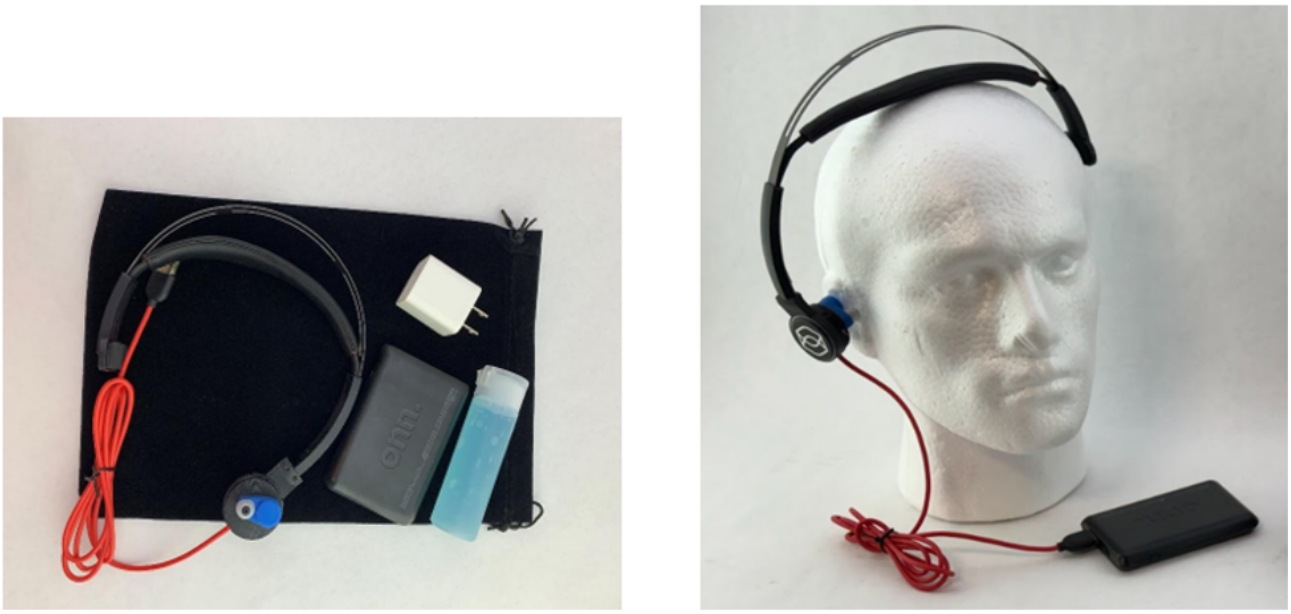
Adults in the United States were recruited through web-based social media advertising mentioning a study investigating a new treatment for anxiety disorders. Interested individuals filled out a study registration form containing only contact information and were then contacted by a member of the research team via email with further details of the study and a link to sign the informed consent. Upon completion of the informed consent, candidates were then screened for inclusion and exclusion criteria using web-based questionnaires. Interested individuals were included if they scored 16 or higher on the BAI, were older than 18 years, and did not have any additional conditions that were contraindications for VNS or ultrasound. Conditions that were contraindications for VNS included a history of vagotomy, heart arrhythmias, schizophrenia, or rapid cycling bipolar disorder. Conditions that were contraindications for ultrasound included presence of a pacemaker, pregnancy, active cancer, decreased sensation or open wounds in the ear, ear infection, or metal implants in or around the ear. A BAI score of 16 was chosen as the cutoff threshold because a score of 16 or higher in the BAI classifies an individual as having moderate to severe anxiety symptoms [34]. We did not exclude individuals who were receiving other treatments for their anxiety as long as the treatment was not initiated or ceased within the past month.

A total of 100 individuals completed the interest form, 63 signed the informed consent and were screened, and 28 were enrolled in the study. Each participant was assigned a unique identifier code so that participant information could be managed in a confidential manner throughout the study and the data could be deidentified upon completion of the study. Only the principal investigator and the study coordinator had access to the unique identifier code assignments.

Ultrasound Device

ZenBud, the device used for this trial, is a proprietary Conformité Européenne–compliant over-the-ear wearable headset that was developed by NeurGear (Figure 1A and B). The ZenBud delivers LIFU to the auricular branch of the vagus nerve through several layers of skin. The ZenBud is designed to mimic a standard headset so that users can integrate the use of the device into their routine with minimal effort and discomfort. When the user plugs the ZenBud device into the battery pack it immediately turns on. There is a hardware limit in the circuitry so that the device shuts down after running for 29 minutes, limiting the duration of use. The ZenBud device specifications include a center frequency of 5.3 MHz, a pulse repetition frequency of 41 Hz, a duty cycle of 50%, and an average intensity of 1.03 MPa.

Figure 1. (A) The ZenBud headset, powerpack, power brick, and bottle of gel. The ultrasound transducer is located in the round earpiece on the right side of the headset. (B) The ZenBud device as depicted properly placed on a model human head.

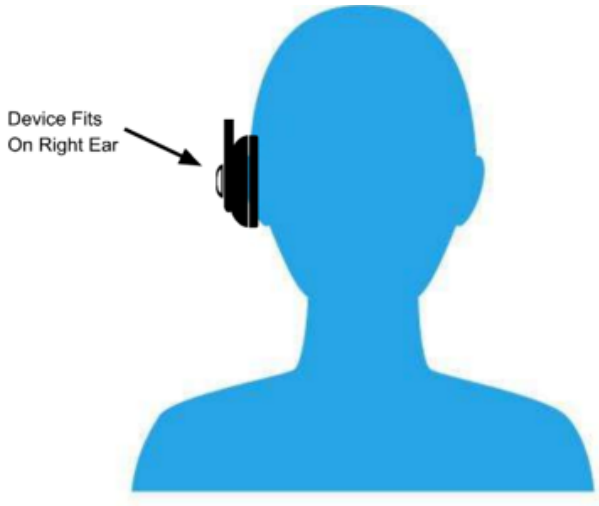


(A) (B)

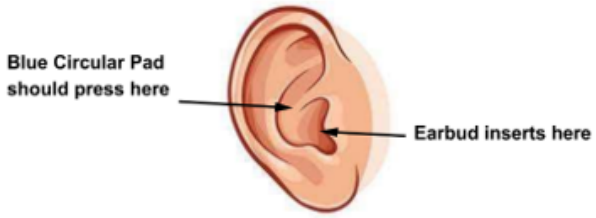
A detailed instruction manual was provided in the package with every device. A copy of the manual is provided as Multimedia Appendix 1. The participants were instructed to use the device once a day for 5 minutes unless instructed otherwise by a health care professional. There were no stipulations set for the time of day that treatment could be completed and participants were free to choose a time that was convenient for them. For step-by-step set up and use, participants were instructed to apply a pea-sized amount of the aqua sonic gel to the blue part of the device located directly above the headset (Figure 2A), position the blue circular pad against the skin just above the ear canal (Figure 2C), adjust the headset until they felt a moderate pressure (without pain) just above the ear canal where the blue circular pad was positioned (Figure 2B), and begin stimulation by plugging the USB cable into the battery pack (Figure 2D). Once the headset is plugged into the battery pack the device starts working and a low humming noise can be heard. The manual instructs users to listen for the humming sound to indicate that the device is working properly.

Figure 2. Images extracted from the ZenBud user manual depicting step-by-step setup and operation of the device. (A) Application of the ultrasonic gel. (B) Placement of the headset with the headset located over the right ear. (C) Correct placement of the headset on the ear. (D) Treatment is started upon inserting the USB cable into the battery pack.

(A)



(B)



(C)

(D)

Data Collection

Assessments were done using a battery of 4 validated clinical outcome measures. These were taken on the day before the first treatment session, weekly, and on the day of the final treatment session after the final treatment session was completed. The following 4 clinical outcome measures were used.

Beck Anxiety Inventory

The BAI is a rating scale used to evaluate the severity of anxiety symptoms in individuals aged 17 years and older. It contains 21 self-report items that reflect common physiological symptoms of anxiety such as numbness or tingling, feeling hot, and trembling. Participants indicate how much they have been bothered by each symptom, from “not at all” to “severely,” using a 4-point Likert scale. The item scores are then summed, with possible scores ranging from 0 to 63. A total score of 0 - 7 is classified as minimal anxiety, 8 - 15 as mild, 16 - 25 as moderate, and 26 - 63 as severe [35,36]. The BAI has a Cronbach α value of 0.91, a good test-retest reliability (κ=0.65, 95% CI 0.61-0.69), and correlates moderately (Pearson *r*=0.51) with the revised Hamilton Anxiety Rating Scale (HAM-A) [34,35,37,38].

Beck Depression Inventory Version II

Depression and anxiety are highly comorbid, with 60% of patients with anxiety disorders also having depression [32]. Long-term activation of the stress response may explain this overlap [39], implying that inhibiting overactivation of the stress response may alleviate depressive symptoms in addition to anxiety and stress. The BDI-II is a valid and reliable self-report measure for depression that quantifies depressive symptoms over the last week [40]. For each of the 21 items, respondents are asked to choose the statement they most agree with out of a group of 4 choices. Each statement corresponds to a score ranging from 0 to 3 and total scores range from 0 to 63 [35,41,42]. The scores are classified as minimal depression (0 - 13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63) [38,41]. The BDI is positively correlated with the Hamilton Depression Rating Scale with a Pearson *r* of 0.71, showing good agreement. The test was also shown to have a high 1-week test-retest reliability (Pearson *r*=0.93), suggesting that it was not overly sensitive to daily variations in mood and high internal consistency (α=.91) [38,41].

PTSD Checklist for DSM-V (PCL-5)

While the *DSM-V* does not classify PTSD as an anxiety-related disorder, both PTSD and anxiety disorders involve dysregulation in neural structures dealing with fear, arousal, and anticipation of future threats [33]. Thus, there is reason to believe that VNS simulation could be beneficial for PTSD-related symptoms. The PCL-5 is a self-report questionnaire that helps assess the presence and severity of PTSD symptoms. The PCL-5 can be used to screen for PTSD, assist in making a provisional diagnosis, and monitor symptoms over time [43] . The measure asks participants to rate how much they were bothered by certain PTSD symptoms over the past month on a 5-point Likert scale ranging from "not at all" to "extremely" [44]. Total scores range from 0 to 60 and scores ranging from 31 to 33 are widely accepted as the cutoff for diagnosing PTSD [45]. In a systematic review of PCL-5 validation studies, Forkus et al [45] concluded that the full 20-item version showed good to excellent internal consistency across studies (Cronbach α values ranging from 0.83 to 0.97) and acceptable temporal stability (correlations ≥0.60) across time points within 1 - 5 weeks of one another. Scores were also moderately to highly correlated with other measures of PTSD as well as measures of anxiety, depression, suicidal ideation, and sleep.

Pittsburgh Sleep Quality Index

Anxiety and sleep disturbance are frequently co-occurring [46] such that sleep disturbance is a *DSM-V* criterion for generalized anxiety disorder. Studies have found correlations between BAI scores and subjective sleep quality among college students [47], indicating that measuring sleep quality could provide insight into the burden of anxiety on well-being. The PSQI is a validated and widely used global measure of sleep quality [48,49]. It comprises 19 self-report items and 5 items to be reported by a sleeping partner, but the 19 self-report items are commonly used on their own in research contexts [50]. The different items call for responses in different formats (bedtimes, number of hours, Likert scales, etc), thus the instrument is scored with the use of 7 component scores that are summed for 1 total score ranging from 0 to 21 [48]. The original creators of the PSQI found that a score of 5 or greater differentiated between "good" and "poor" sleepers, with a sensitivity of 89.6% and a specificity of 86.5% [48]. Research since has generally supported the validity of this cutoff. Mollayeva et al [49] did a meta-analysis of the psychometric properties of the PSQI and found that it showed acceptable internal reliability for within-group comparisons across studies (Cronbach α values ranging from 0.70 to 0.83). They also found that intraclass correlations for PSQI scores across timepoints met the cutoffs for use in within-group comparisons (0.70 or greater) [49].

Exit Survey

In addition to the clinical outcome measures, participants also completed an exit survey on the final day of the trial. This survey asked questions regarding overall satisfaction with the treatment, impact on daily functioning and quality of life, ease of use, symptom improvement, side effects, and how quickly effects from the treatment were perceived to be felt. The purpose of this questionnaire was to provide further insight into the perceived experiences of the participants during the treatment period, which is important information for full and complete understanding of the treatment's impact.

Adverse Event Tracking

Adverse events (AEs) and device deficiencies were documented and categorized in accordance with ISO14155:2020. These AEs were documented based on reports provided by the participants through email or on the exit survey. The investigators closely tracked the AEs and their resolution throughout the study. Each AE was categorized by type and seriousness according to the definitions provided in ISO14155. Whether an AE was related to the device or procedures was also distinguished. All available details for each AE were recorded in the participant case report forms, including relationship to the investigational device, severity (mild, moderate, or severe), onset date, resolution status, any action taken, and if there were any sequelae. For the causality assessment of all AEs, the MDCG 2020-10/1 guideline was followed. This guidance is specifically aimed at severe adverse events; however, it was extrapolated to all AEs for this study.

According to MDCG 2020-10/1, causal relatedness was defined as an AE associated with the investigational device beyond reasonable doubt. Probably device-related was defined as having a relationship with the use of the investigational device that seems relevant or the event cannot be reasonably explained by another cause. "Possibly device related" was defined as having a relationship with the use of the investigational device that was weak but cannot be ruled out completely. "Not device related" was defined as an event not having a temporal relationship with the device or not following a known response pattern to the device. The AEs were then further classified into mild, moderate, or severe categories. Mild severity AEs correspond to awareness of easily tolerated and mildly irritating signs or symptoms, with no or minimal loss of time from normal activities; these symptoms are transient and do not require therapy or a medical evaluation. Moderate cases are events that introduce a low level of inconvenience or concern to the participant and may interfere with daily activities; moderate experiences may cause some interference with functioning. Severe cases are events that substantially interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; these events are usually incapacitating.

Statistical Analysis

The primary and secondary end points of the study are thoroughly described in the "Data Collection" section. These end points included pre- to posttreatment changes from baseline to the end of treatment at 4 weeks for the BAI as the primary end point and the BDI, PCL-5, and PSQI as secondary end points. Baseline scores were defined as the BAI, BDI, PCL-5, and PSQI scores on the first day of treatment, prior to the first treatment session. The within-group analyses were based on a per-protocol estimand and tested with paired 2-tailed *t* tests, where the normality assumption was confirmed with the Shapiro-Wilk test and α value was set to .05. The effect sizes reported in this paper are based on Cohen *d* and calculated as the mean score at the end of treatment minus the mean score at baseline, divided by the pooled SD for the 2 scores. The use of

per-protocol estimand ensured that the changes in outcome measures within each treatment arm were reflective of scenarios where the participants used the treatment as directed and thus included only the participants who were compliant to treatment. The usage criteria for inclusion in the per-protocol analysis was set at 5-29 minutes of treatment per day 6-7 days per week across the intended 4-week treatment period. There were only 2 missing scores, 1 in week 2 and 1 in week 3. Because these data are a time series that exhibits a trend line and the number of missing values was very small, these were filled using a linear interpolation between the score from the previous week and the score from the following week. There was no missing baseline or final scores.

To determine the appropriate sample size a power analysis was performed assuming a dependent *t* test with a significance level of 5%, power of 80%, and moderate effect size of 0.6 between pairs. This gave us a necessary sample size of 25 participants. Accounting for a potential dropout rate of 20% gave us a target sample size of 30 participants. All analyses were performed using GraphPad Prism 10.3.0 (507; Dotmatics).

Ethical Considerations

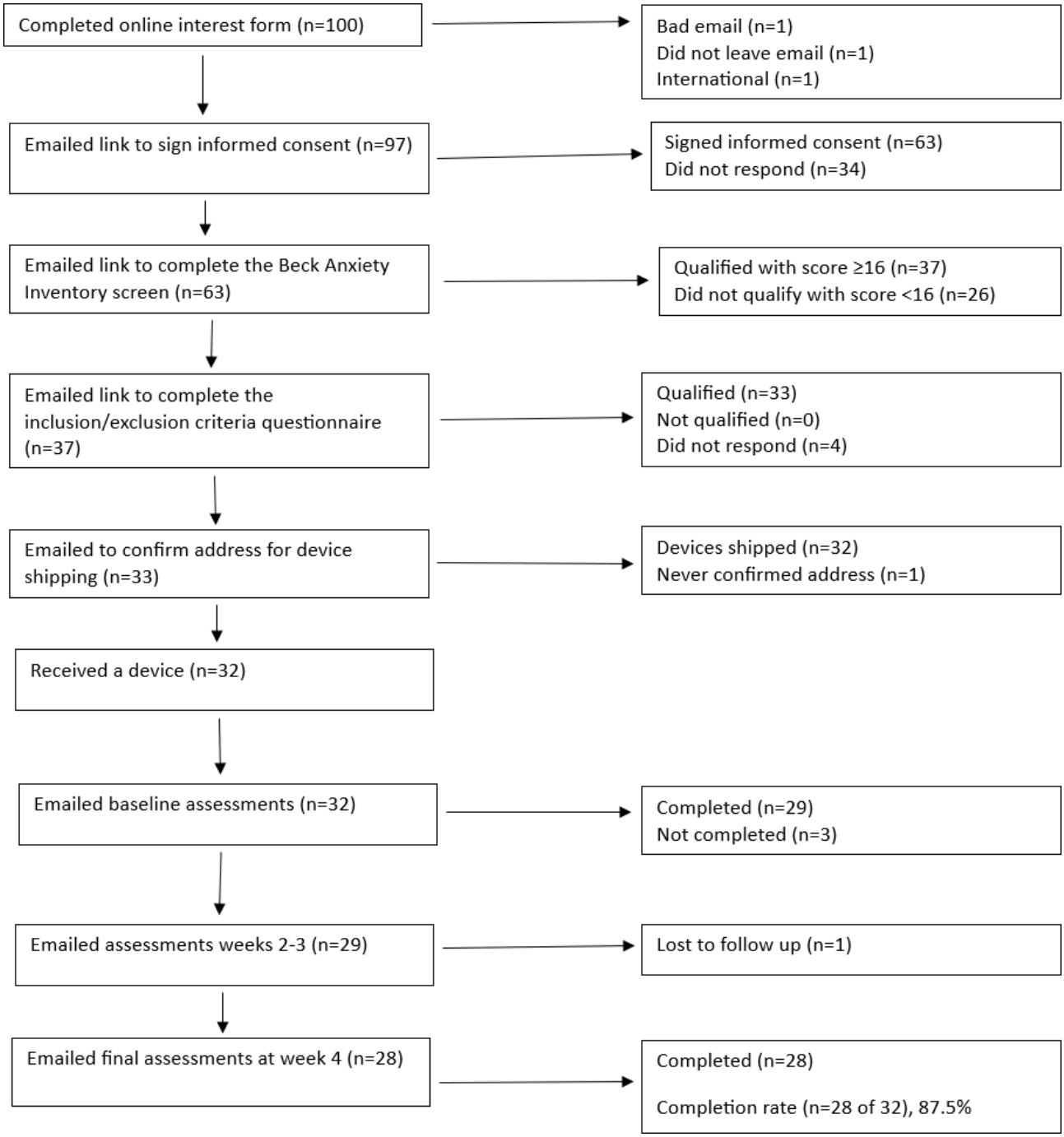
Ethical approval for this trial was obtained from the WIRB-Copernicus Group (WCG) institutional review board (reference no. 20233919), and the study was conducted in compliance with the principles outlined in the Declaration of Helsinki. Signed and documented informed consent was obtained from all participants prior to starting the study. For their time, participants were given a US $25.00 Amazon gift card.

Results

Study Participants

Between October 22, 2023, and October 2, 2024, 100 individuals completed the web-based interest form (Figure 3). A total of 63 participants consented to the trial, with 26 of these not satisfying the criteria of having a BAI score of 16 or greater, 4 not responding to requests to complete the screening questionnaire, and 1 not responding to requests for confirmation of their shipping address. A total of 32 participants were shipped a device, with 3 of these not responding to requests to complete the baseline assessments and 1 participant failing to respond to requests to take the reassessments after week 2. In total, 28 participants completed all LIFU sessions and weekly assessments (28/32, 87.5%). Data for all 28 participants who completed the trial are included in the analysis.

Figure 3. Flowchart of study participants through the trial.



The average age of the participants was 48.1 (SD 15.6) years. The group was heavily weighted toward women, with 22 women and 6 men. The National Institutes of Health reports that generalized anxiety affects approximately 2.7% of American adults, with women experiencing the disorder at a higher rate (3.4%) versus men (1.9%), making the fact that the sample contained a higher percentage of women a reflection of actual population distributions. The self-reported average duration of time suffering with anxiety was 16.5 (SD 11.8) years. There were also 8 participants currently receiving treatment for their anxiety and 20 who were not receiving any treatment.

Beck Anxiety Inventory

After 4 weeks of treatment with the ZenBud, the average BAI score decreased by 14.9 (SD 10.6) points from 26.5 (SD 12.5) to 11.5 (SD 11.1) (Figure 4). This change in score was both statistically significant (P<.001, 2-tailed dependent t test) and clinically meaningful. While there is no consistently defined definition of clinical improvement for the BAI, based on the categorical definitions of severity for the scores, there was a great deal of progression into decreased severity levels of anxiety throughout the treatment period. As seen in Figure 5, at the start of the study, 22 participants had BAI scores in the moderate or severe anxiety ranges and only 6 participants had BAI scores in the mild or minimal severity ranges. After 4 weeks of using the ZenBud, 22 participants had BAI scores into the mild or minimal severity rages, and only 6 participants had scores in the moderate or severe ranges. In terms of Cohen d, the effect size was large at 1.06.

Figure 4. The progression of Beck Anxiety Inventory scores through 4 weeks of treatment with ZenBud. The thin lines represent each individual participant. The thick line represents the group mean.

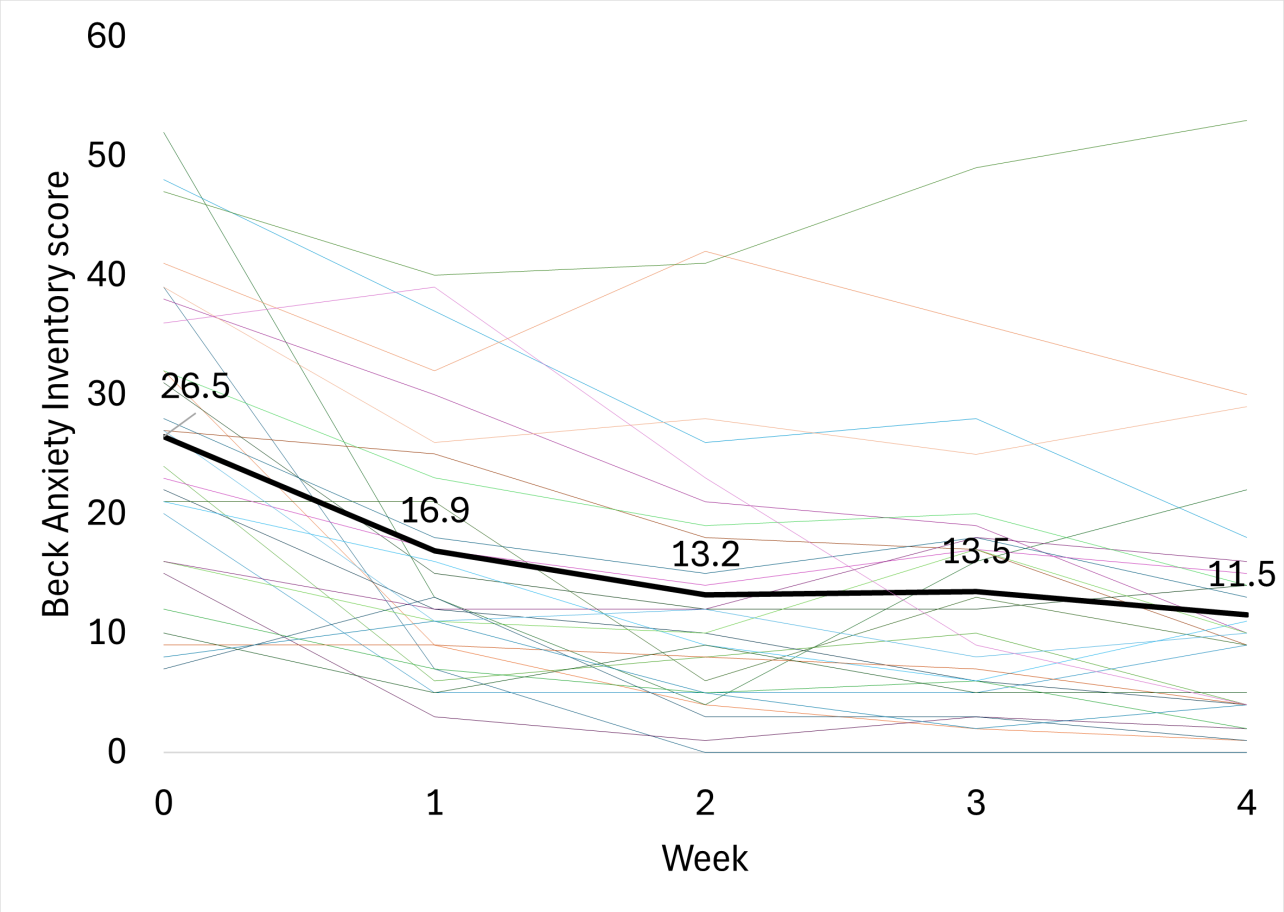
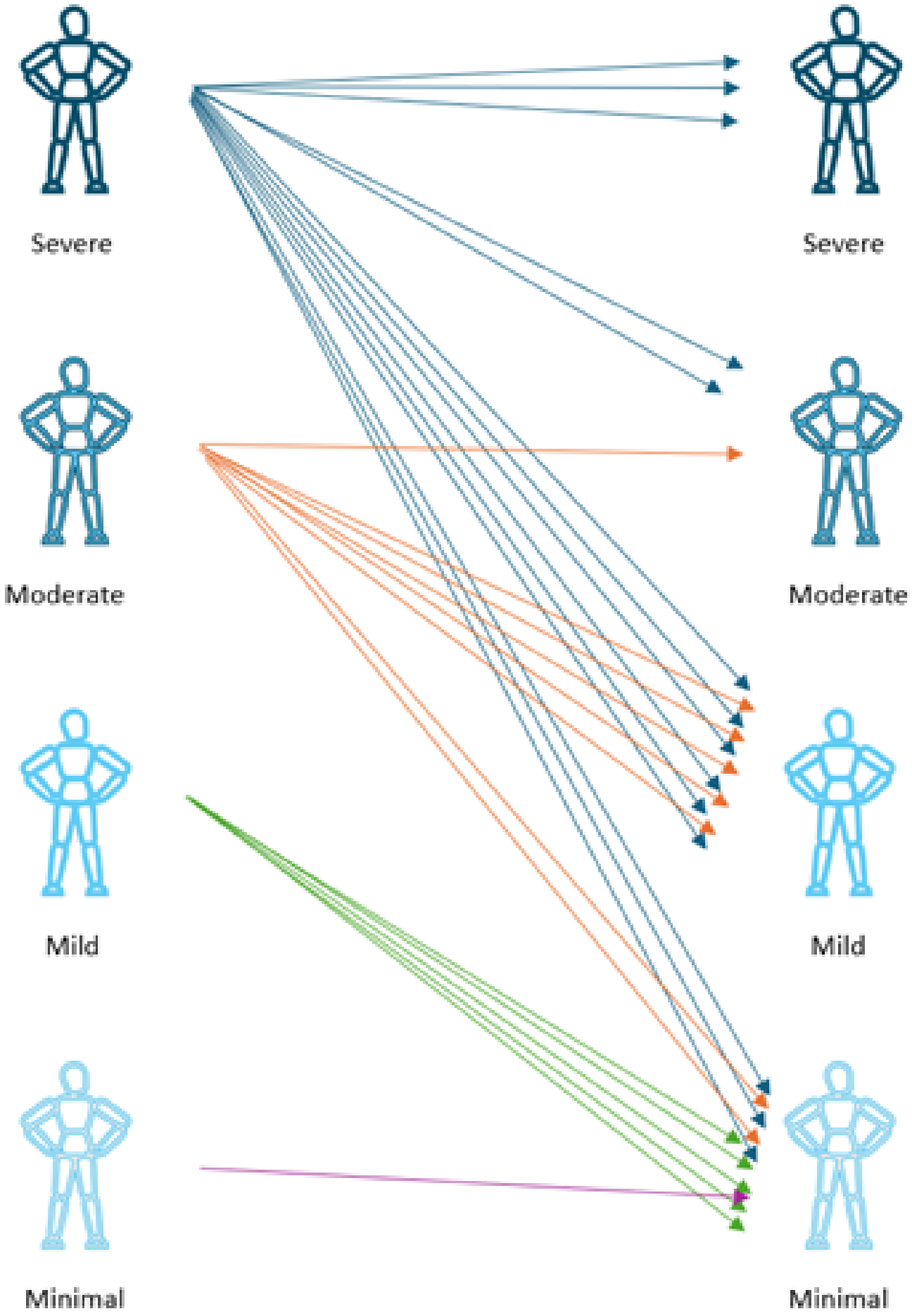


Figure 5. Categorical movement across degrees of severity based on the Beck Anxiety Inventory (BAI) definitions. At the start of the study, 20 participants had BAI scores in the moderate or severe anxiety ranges and only 6 participants had BAI scores in the mild or minimal severity ranges. After 4 weeks of using the ZenBud, 20 participants had BAI scores into the mild or minimal severity ranges, and only 6 participants had scores in the moderate or severe ranges.



Beck Depression Inventory

After 4 weeks of treatment with the ZenBud, the average BDI score decreased by 10.3 (SD 7.8) points from 24.2 (SD 10.5) to 13.9 (SD 12.6) (Figure 6). Similar to results seen for the BAI, this change in score was both statistically significant (P<.001; 2-tailed dependent t test) and clinically meaningful. A 17% reduction in score on the BDI is considered clinically meaningful [3]. Based on this definition, as seen in Table 1, 71.4% (20/28) of participants demonstrated a clinically meaningful reduction in score by the end of the trial. In terms of Cohen d, the effect size was large at 0.81.

Figure 6. The progression of Beck Depression Inventory scores through 4 weeks of treatment with ZenBud. The thin lines represent each individual participant. The thick line represents the group mean.

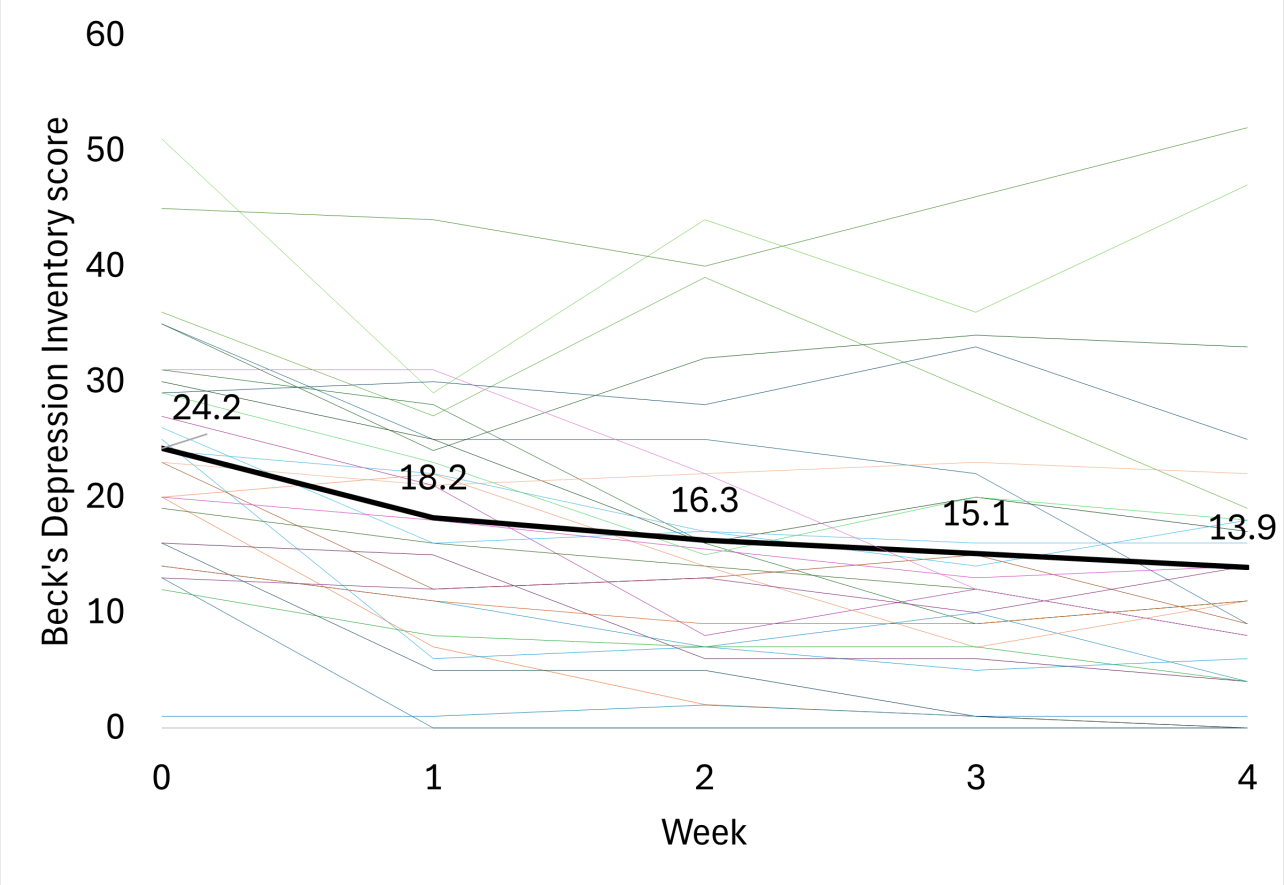


Table . The number of participants who experienced clinically significant reductions in Beck Depression Inventory score following 4 weeks of treatment with the ZenBud.

Degree of score change	Participants, n (%)
Clinical decrease	20 (71)
Nonclinical decrease	5 (18)
Nonclinical increase	3 (11)

Post Traumatic Stress Disorder Checklist for the *DSM-V*

After 4 weeks of treatment with the ZenBud, the average PCL-5 score decreased by 20.0 (SD 20.5) points from 38.8.8 (SD 18.0) to 18.8 (SD 18.9) (Figure 7). Similar to results seen for the BAI and BDI, this change in score was both statistically significant (P<.001; 2-tailed dependent t test) and clinically meaningful. A 10-point reduction in score on the PCL-5 is considered clinically meaningful [43,51]. Based on this definition, as seen in Table 2 , 71.4% (20/28) of participants demonstrated a clinically meaningful reduction in score by the end of the trial. In terms of Cohen d, the effect size was large at 0.94.

Figure 7. The progression of PCL-5 scores through 4 weeks of treatment with ZenBud. The thin lines represent each individual participant. The thick line represents the group mean.

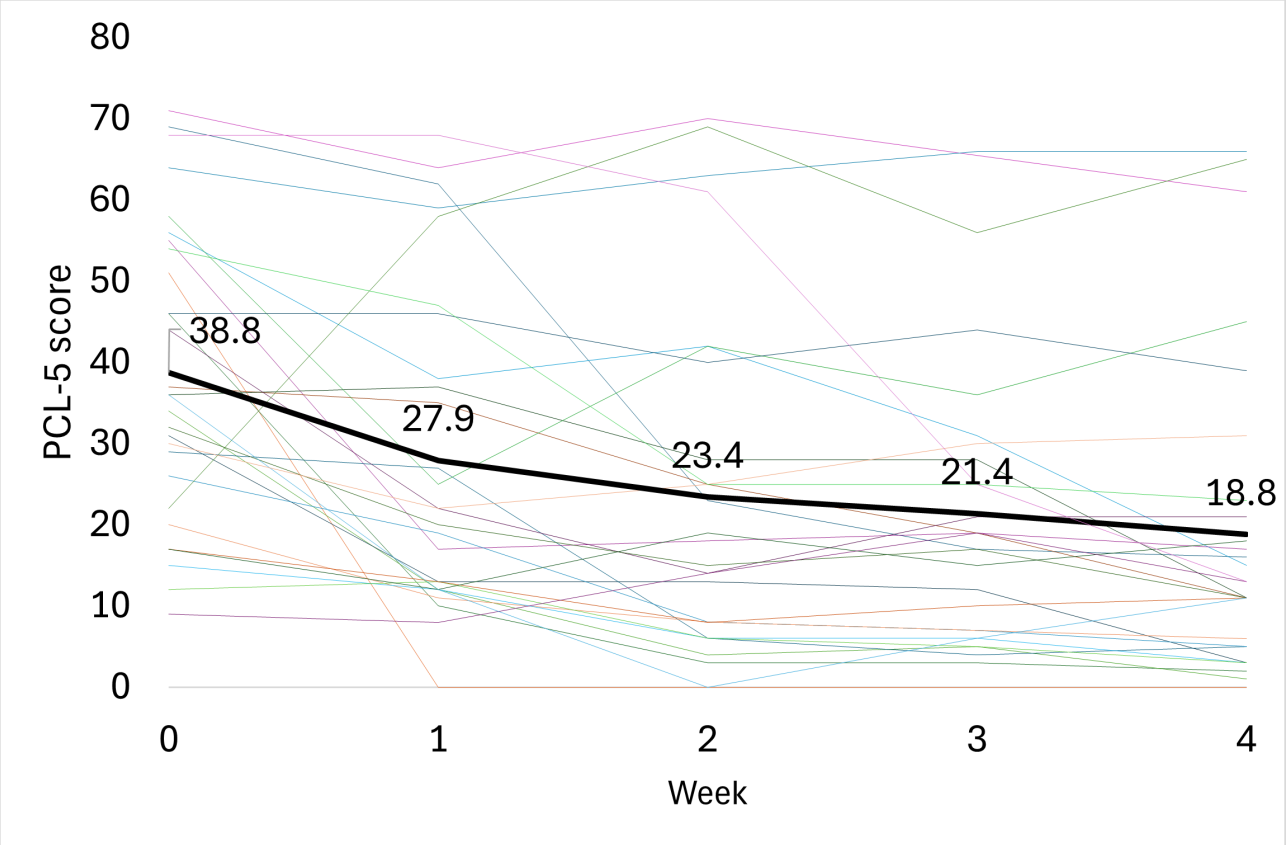


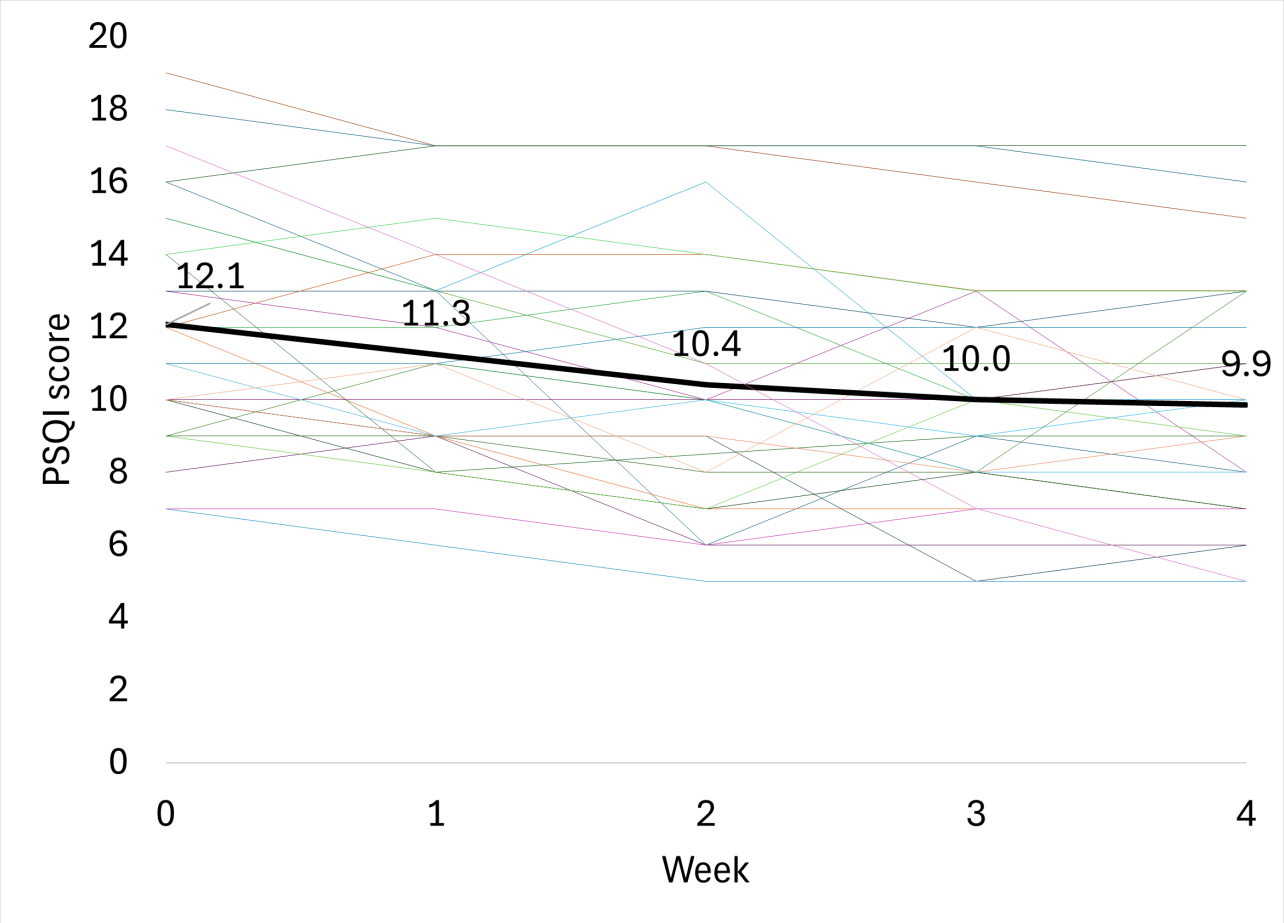
Table . The number of participants who experienced clinically significant reductions in PCL-5 score following 4 weeks of treatment with the ZenBud.

Degree of score change	Participants, n (%)
Clinical decrease	20 (71)
Nonclinical decrease	3 (11)
Nonclinical increase	4 (14)
Clinical increase	1 (4)

Pittsburgh Sleep Quality Index

After 4 weeks of treatment with the ZenBud, the average PSQI score decreased by 2.2 (SD 3.1) points from 12.1 (SD 3.2) to 9.9 (SD 3.2) (Figure 8). While this change in score was statistically significant (P=.001; 2-tailed dependent t test), it was not clinically meaningful. In terms of Cohen d, the effect size was medium at 0.65.

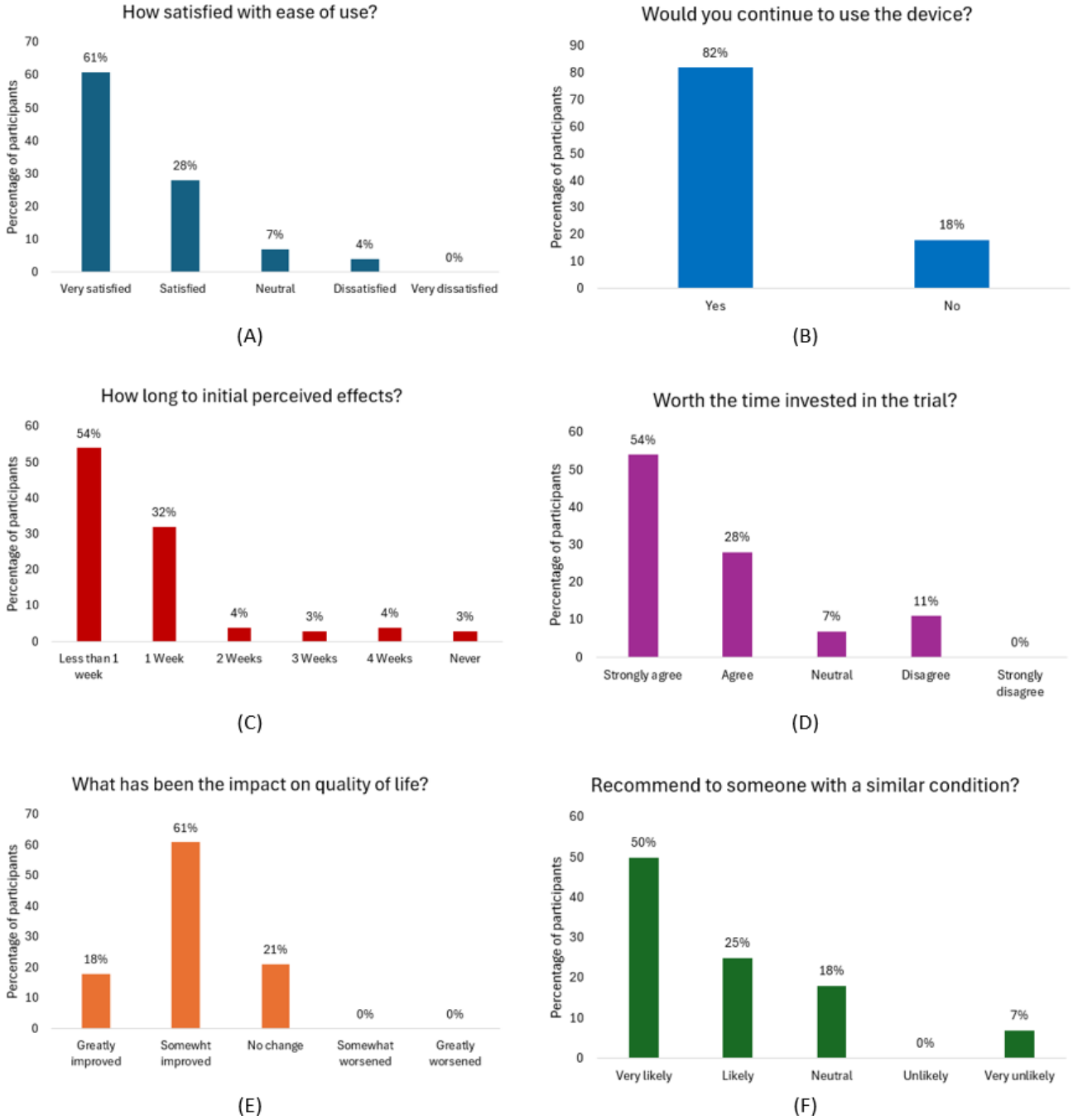
Figure 8. The progression of PSQI scores through 4 weeks of treatment with ZenBud. The thin lines represent each individual participant. The thick line represents the group mean. PSQI: Pittsburgh Sleep Quality Index.



Satisfaction and Acceptability

After the final treatment and assessment, battery participants completed an exit survey asking questions regarding satisfaction with the treatment, acceptability, and quality-of-life impact. When asked about satisfaction with ease of use, 89.3% (25/28) of participants responded with very satisfied or satisfied (Figure 9A). In addition, 82.1% (23/28) of participants reported that they would continue using the device if offered the opportunity (Figure 9B). When asked whether the treatment was worth the time invested in the trial, 82.1% (23/28) of participants strongly agreed or agreed that the time invested was worth it (Figure 9D). When asked about the impact on quality of life, 78.6% (22/28) of participants reported that the treatment somewhat or greatly impacted their quality of life (Figure 9E). When asked how long it took to feel initial effects, 53.6% 15/28) of participants noticed effects in less than 1 week and 32.1% (9/28) felt initial effects by 1 week (Figure 9C). When asked whether they would recommend the treatment to someone with a similar condition, 75.0% (21/28) of participants responded with very likely or likely (Figure 9F).

Figure 9. Results of the exit survey. (A) Responses of the participants when asked "How satisfied were you with the ease of using the device?" (B) Responses of the participants when asked "Would you continue using this device for treatment?" (C) Responses of the participants when asked "How quickly did you feel the effects of the ZenBud device during your trial?" (D) Responses of the participants when asked "Do you feel the device was worth the time invested in the trial?" (E) Responses of the participants when asked "How did the device impact your overall quality of life?" (F) Responses of the participants when asked "How likely are you to recommend this device to others with similar conditions?."



Adverse Events

Only 1 AE was reported throughout the duration of the trial. On the exit survey following completion of the 4 weeks of treatment, 1 participant reported that the treatment would make them feel jittery for a short period of time afterward. This effect was short-lived and classified as a mild AE that was probably device related. The participant reported that this side effect was not enough of an effect to make them stop treatment or drop out of the study. Overall, the high satisfaction rates as described in the "Satisfaction and Acceptability" section combined with the low rate of AE support a strong benefit-to-risk profile for the ZenBud. However, this study was done with a small sample size and these results need to be further validated with a larger sample size.

Discussion

Principal Findings

The main objective of this study was to provide preliminary evidence of the efficacy, safety, and usability of the ZenBud for treating symptoms of anxiety in humans. Overall, the study represents one of the first clinical trials supporting the safety,

patient tolerability, and efficacy of using LIFU to the auricular branch of the vagus nerve for the treatment of anxiety symptoms.

Among the 28 participants, 92.9% (26/28) demonstrated improvements in anxiety symptoms, 89.3% (25/28) demonstrated improvements in depression symptoms, 82.1% (23/28) demonstrated a reduction in symptoms of PTSD, and 65.5% (18/28) demonstrated improvements in sleep quality after 4 weeks of treatment. The average score reduction on the BAI was clinically meaningful at 14.9 points (SD 10.6, $P<.001$; 2-tailed dependent *t* test), reflecting a general movement from severe anxiety symptoms to mild [35,36]. The average score reduction on the BDI was clinically meaningful at 10.3 points (SD 7.8, $P<.001$; 2-tailed dependent *t* test), which was a 42.6% decrease in score, far greater than the 17% clinically meaningful threshold [3]. The average score reduction on the PCL-5 was clinically meaningful at 20.0 points (SD 20.5, $P<.001$; 2-tailed dependent *t* test) [43]. It is also noteworthy to mention that the PCL-5 is commonly used to determine whether an individual meets a provisional diagnosis of PTSD and requires further assessment to confirm the diagnosis. The cutoff score for meeting the criteria for a provisional PTSD diagnosis is 31 - 33. Based on using a cutoff score of 32, at the start of the study 18 participants exceeded the threshold score for a provisional PTSD diagnosis. Upon completion of the study, 14 of these participants (77.8%) had dropped their score below the threshold score of 32 and no longer met the requirements for a provisional PTSD diagnosis. The average score reduction on the PSQI was 2.2 (SD 3.1, $P=.001$; 2-tailed dependent *t* test) which, while statistically significant, was not clinically meaningful, indicating that the improvements in anxiety, depression, and PTSD symptoms did not carry over into improved sleep quality. The effect sizes were also large for the BAI (Cohen $d=1.06$), BDI (Cohen $d=0.81$), and PCL-5 (Cohen $d=0.94$) indicating that the observed score improvements were substantial enough to have a meaningful impact beyond just statistical significance.

The extent of improvement in anxiety, depression, and PTSD observed in this study is comparable with the clinically meaningful results reported in other clinical trials featuring noninvasive VNS as a treatment intervention. Srinivasan et al [52] conducted a randomized controlled trial of taVNS with 60 retired schoolteachers who had been diagnosed with anxiety during the COVID-19 pandemic. The participants did 30-minute sessions 4 times per week (16 total sessions) and demonstrated significantly greater reductions in Generalized Anxiety Disorder-7 (GAD-7) scores and salivary cortisol levels compared with control group participants. Zhang et al [53] investigated the effect of taVNS on anxiety symptoms and neural functioning in 30 individuals with Parkinson disease and anxiety compared with 30 controls with no anxiety. They treated patients with Parkinson disease with taVNS for 2 weeks and measured progress using the HAM-A and nerve activation in the bilateral prefrontal cortex during a verbal fluency task. After 2 weeks of taVNS treatment, the group demonstrated a significant decrease in HAM-A scores ($P<.001$) and increased activation of the left triangle portion of the inferior frontal gyrus. Ferreira et al [54] treated college students with chronic anxiety with a week of taVNS. Immediately postintervention and 2 weeks postintervention the students demonstrated substantial reductions in pain perception, Beck Anxiety Inventory scores, and masseter activation. Rong et al [55] treated 91 patients with mild to moderate depression with taVNS for 30 minutes twice a day for 12 weeks. Upon completion of treatment the average reduction in score in the 24-item Hamilton Depression Rating Scale (HAM-D-24) was both statistically significant and clinically meaningful, the responder rate was 80%, and the remission rate was 39%. In our study, we saw similar results in only 4 weeks, making an investigation into longer treatment periods with LIFU an important area of future research.

The results of this study are also consistent with the results of studies investigating the use of transcranial focused ultrasound (tfUS) targeting the amygdala for the treatment of generalized anxiety disorders. Mahdavi et al [56] recruited 25 participants with treatment-refractory generalized anxiety disorder and treated them with tfUS targeting the right amygdala for 8 weekly 10-minute sessions. The results showed an average reduction in BAI score of 12.88 (SD 10.42) points and an average reduction in HAM-A scores of −12.64 (SD 12.51). Chou et al [57] recruited 30 healthy individuals and compared activation of the amygdala, hippocampus, and dorsal anterior cingulate cortex during a fear task after treating them with active or sham tfUS targeting the left amygdala. They found decreased activation of the amygdala ($P=.04$), hippocampus ($P=.05$), and dorsal anterior cingulate ($P=.02$) in the active tfUS group when compared with the sham. They also found decreased amygdala-insula ($P=.03$) and amygdala-hippocampal ($P=.01$) resting state functional connectivity and increased amygdala-ventromedial prefrontal cortex ($P=.05$) resting state functional connectivity.

Limitations

While the results of this study are optimistic, this study was preliminary and suffers from several limitations. This study did not feature a control group, making it impossible to quantify the possible impact of a placebo effect or distinguish the specific effects of the ZenBud device from other factors that may have influenced the results. The lack of a control group also limits the ability to directly compare the efficacy of the ZenBud with other interventions. Other than participant reports, there was also no objective way of determining the exact amount of time the device was used by each participant. While the majority of participants were not receiving treatment during the study, there was no control over concurrent therapeutic modalities participants were receiving. The lack of control for these additional therapies may have influenced the results, making it difficult to attribute the observed effects exclusively to the ZenBud device. Further research with larger sample sizes, control groups, control over concurrent treatment modalities, and physiological measurements needs to be done to validate these findings and further negate the possibility of placebo effects.

Conclusions

This preliminary study provided justification for further research into the efficacy, safety, and feasibility of using LIFU to modulate the auricular branch of the vagus nerve and reduce the symptoms of anxiety, depression, and PTSD. Given the wide prevalence of anxiety disorders, depression, and PTSD,

and the shortfalls of current treatment options, this novel treatment approach has potential to meaningfully improve patient outcomes and continued research is warranted.

Conflicts of Interest

IK is the chief science officer for NeurGear. JH is the chief executive officer for NeurGear. EM declares no conflicts of interest.

Multimedia Appendix 1
ZenBud user manual.
[PDF File, 1446 KB - neuro_v4i1e69770_app1.pdf]

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Abbreviations

AE: adverse event
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
***DSM-V*:** *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)
HAM-A: Hamilton Anxiety Rating Scale
LIFU: low-intensity focused ultrasound
PSQI: Pittsburgh Sleep Quality Index
PTSD: posttraumatic stress disorder
SNS: sympathetic nervous system
taVNS: transcutaneous auricular vagal nerve stimulation
tfUS: transcranial focused ultrasound
VNS: vagus nerve stimulation

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Experiences of a Neurofeedback-Based Mindfulness Meditation Intervention for Migraine: Qualitative Study

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Abstract

Background: Migraine is a debilitating neurological condition often impacting the quality of life and resulting in physical, emotional, and social burdens. Pharmaceutical interventions are the conventional treatment for migraine; however, behavioral interventions provide safe alternatives. Both mindfulness meditation and neurofeedback are behavioral interventions that have been separately studied for migraine treatment. To date, no studies have investigated neurofeedback-assisted mindfulness meditation for migraine treatment and prevention.

Objective: The objective of our study was to document the experiences of individuals with migraines who participated in an 8-week neurofeedback-based mindfulness meditation intervention as part of a randomized controlled trial.

Methods: Semistructured interviews were undertaken with 10 participants (7 female and 3 male participants) aged 23 to 55 years who had previously completed an 8-week neurofeedback-based mindfulness meditation program using Muse wearable sensory headbands as part of a randomized control trial. The interview data were analyzed using reflexive thematic analysis.

Results: Participants spoke to 3 categories of experiences: the positive impact of neurofeedback-based mindfulness meditation on migraine experiences, enhanced well-being and improved quality of life resulting from the intervention, and the benefits and drawbacks of incorporating a portable electroencephalogram technology into mindfulness meditation practices in the context of migraine treatment. In total, 9 participants felt that their ability to manage migraine symptoms was improved, and all participants expressed benefits beyond migraine prevention and pain management. Participants also spoke to the interconnectedness of migraine symptoms, daily stressors, and the framing of lived experience.

Conclusions: Notably, as the first study to evaluate the experiences of individuals with migraines using an at-home, neurofeedback-based mindfulness meditation intervention, this investigation adds to our understanding of nonpharmaceutical migraine treatment. Participants reported that this neurofeedback-based mindfulness meditation intervention improved migraine management, leading to significant reductions in pain intensity, migraine frequency, and medication use. They also described improved quality of life and emotional regulation related to this intervention, which they attributed to enhanced attentional control and body awareness. This research supports the consideration of neurofeedback-based mindfulness meditation interventions using emerging technologies, such as wearable electroencephalogram devices, as an accessible behavioral intervention for migraine management.

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KEYWORDS

migraine; mindfulness; meditation; neurofeedback; behavioral intervention; mobile health; qualitative; headache

Introduction

Background

Migraine, a debilitating neurological condition, manifests as recurrent attacks of moderate to severe pulsating head pain that is often localized to one side of the head and can last hours to days [1-3]. Symptoms include nausea, vomiting, and sensitivity to light and sound [2-4]. It is estimated that 14% of the world's population and 8.3% of Canadian people experience migraine [3], negatively impacting quality of life and interfering with activities of daily living [2,5,6]. It is also frequently associated with emotional and social burdens, including mood disturbances, social isolation, anxiety, and challenges in work, family, and social contexts [5-8]. Migraine is one of the 2 leading causes of years lived with disability in high and middle sociodemographic index countries and one of the 5 leading causes of years lived with disability globally, with an average prevalence in 2016 of 1.04 billion [9].

Prescription and over-the-counter medications are the conventional abortive and preventive treatments for migraine [10]. Unfortunately, these medications come with negative side effects such as dizziness, drowsiness, nausea, and the risk of

developing medication overuse headaches—classified as overuse of therapeutic medication leading to chronic headache symptoms in individuals prone to migraine [10-13]. Behavioral migraine treatments such as neurofeedback and mindfulness practices may offer safe and effective alternatives or complements to medication [14,15].

Mindfulness-based practices involve purposefully directing one's attention to the present moment and the experience of various sensory, emotional, and cognitive events with an attitude of nonjudgment, curiosity, and acceptance [16-18]. Mindfulness-based interventions are popular and effective behavioral interventions for migraine [19]. Quantitative, mixed methods, and qualitative studies have reported significant decreases in migraine pain intensity [20,21], frequency [4], and medication use [22] associated with these interventions. In a recent unblinded trial, participants reported reduced monthly migraine days and acute medication use after a 10-day mindfulness meditation retreat [23]. A longitudinal study by Grazzi et al [24] argued that mindfulness-based treatments were comparable in effectiveness to prophylactic medication use among individuals with medication overuse headaches in terms of headache frequency and medication intake. The psychosocial benefits of mindfulness meditation are also evident among individuals with migraine, including reduced migraine-related disability [23-25], improved quality of life [26], and increased pain tolerance [27].

While effective, mindfulness meditation has a few limitations as a treatment for migraine. Mindfulness meditation is a time-intensive intervention; research suggests that an effective "dose" requires a daily practice of 20 minutes or more [10,28]. Individuals with migraine may also struggle to access trained educators and service providers or to locate evidence-based resources to develop effective mindfulness meditation skills [29]. The plethora of resources available to consumers, coupled with the intangible nature of mindfulness meditation practice and difficulties documenting skill progression (particularly among beginners), can also serve as barriers to successfully implementing mindfulness meditation to treat migraine pain [30]. Researchers also note that a lack of clarity around ideal dosage patterns, session durations, delivery methods, and responder characteristics continues to hamper this treatment approach [4].

Neurofeedback involves observing real-time displays of brain activity (typically using an electroencephalogram [EEG]) and learning how to alter one's brain activity to achieve a calmer state [28]. Widely used in clinical practice for migraine [19], review papers have noted a relationship between EEG-based neurofeedback programs and improvements in migraine frequency, pain intensity, and indicators of disease burden, such as fatigue and anxiety [31,32]. Recent quasi-experimental studies have also reported significant reductions in pain [33], stress, and anxiety [34] as well as improved sleep quality in individuals with migraine [35] related to neurofeedback. Moreover, studies have suggested that clients using both neurofeedback and medication are more successful in reducing migraine frequency compared to those using medication alone [34].

However, existing research has been limited by high protocol heterogeneity [36], and review studies suggest that it is unclear which neurofeedback protocols would best suit particular patients with chronic pain [31]. Consequently, scholars recommend integrating neurofeedback with other interventions, like relaxation training or mindfulness meditation, mainly because the integration of such techniques is shown to regulate cortical activities, resulting in an improved headache experience [37,38]. Neurofeedback-assisted meditation regimes are seen as promising approaches to address neurofeedback delivery heterogeneity [39]. However, research in this area is limited. Although a meta-analysis by Darling et al [40] provided moderate support for the use of neurofeedback-assisted relaxation training in treating migraine conditions in pediatric patients, the included studies were limited, in that few studies were migraine-specific and were dated [40]. Neurofeedback-assisted meditation training for migraine in adults remains largely unexplored.

The use of neurofeedback for migraine treatment is also limited by various pragmatic challenges, including the availability of trained service providers and specialized equipment and notable time demands. Effective sessions take up to an hour at a time, and treatment protocols include numerous weekly visits over the course of several months [19,41]. Thus, it can be a costly and time-consuming treatment option. Further, high treatment heterogeneity and patient training protocols and objectives that are arguably even more intangible than those associated with mindfulness-based practices (focusing on the breath is slightly more concrete than modulating one's brain activity) represent additional barriers to effectively implementing this therapeutic approach [30,31,36].

In short, mindfulness meditation and neurofeedback are both thought to benefit people with migraine and may have additive value when used together as an alternative or complement to medication. However, the success of these treatments depends on regular practice, access to trained instructors, and evidence-based information, and in the case of biofeedback, regular use of specialized equipment [15,42,43]. Financial costs, time constraints, and access issues represent significant barriers to the widespread use of behavioral migraine interventions. Despite widespread recommendations for combining their use and optimism over the efficacy of combined protocols, no studies to date have investigated the use of mindfulness meditation with neurofeedback in treating adults with migraine. Further, there is little consensus regarding best practices in using neurofeedback, mindfulness meditation, or a combined protocol to treat migraine or which patients might benefit most from these interventions. Although rapidly evolving portable technologies are making behavioral interventions more accessible to people with migraine, additional research on user expectations, experiences, and preferences, clinical outcomes, and best practices is needed to better appreciate whether these technologies are meeting the needs and health objectives of the diverse migraine experience.

This Study

This study is part of a broader program of research on the impact of at-home neurofeedback-assisted mindfulness meditation on

the migraine experience. At-home neurofeedback-assisted mindfulness meditation facilitates learning through guided sessions and feedback on brain states and encourages treatment adherence through records of session history and progress in attaining meditative states over time [44]. In doing so, this at-home intervention has the potential to address access issues and overcome some of the limitations of standalone consumer-grade neurofeedback or mindfulness meditation [19,30,31,36]. In this retrospective qualitative study, we interviewed individuals with migraine who had completed an 8-week neurofeedback-based mindfulness meditation intervention using a portable system for neurofeedback mindfulness training as part of a randomized controlled trial [45]. Qualitative investigations are increasingly being used to complement RCTs and provide a deeper understanding of intervention experiences, acceptability, meanings, and processes [46,47]. In line with this, the aim of this study was to ascertain how adults with migraine experienced an at-home neurofeedback-assisted mindfulness meditation practice, its perceived impact on migraine symptoms, and how it affected their daily lives and coping. We also explored how this intervention impacted participants' quality of life and ability to complete activities of daily living. Participants were queried about the benefits and limitations of the intervention and whether they had continued engaging in mindfulness meditation with neurofeedback after the intervention period. In what follows, we delineate the process of making sense of the experiences of individuals with migraine with an at-home neurofeedback-based mindfulness intervention.

Methods

Ethical Considerations

This study was approved by the Human Ethics Research Board at the University of Saskatchewan (REB 1987). All participants provided informed written consent prior to data collection. Participants were informed of their right to withdraw from the study at any time throughout the trial. To protect participant privacy, all data were deidentified, stored on secure, password-protected servers, and accessible only to authorized research personnel. After data collection, participants received a debriefing summary outlining the study's purpose and procedures. As compensation for their time and participation, individuals were allowed to keep the portable neurofeedback devices used during the study.

Participants

Participants were recruited from a larger group of 64 individuals with migraine who had participated in a study of the effects of a neurofeedback-based mindfulness meditation intervention with Muse on migraine severity, migraine disability, headache management self-efficacy, and comorbid psychiatric disorders. This group consisted of adults with either a migraine diagnosis or headache symptoms that met the International Classification of Headache Disorders [1] criteria for migraine disorder who had smartphone and internet access. Of these, 33 completed a neurofeedback-based mindfulness meditation task, and 31 completed an attention control task. Exclusion criteria included having started a new preventive medication within the last 6 months [48], comorbidity of Raynaud syndrome or diabetes, and previous engagement in meditation practices (ie, regular meditation sessions exceeding 60 minutes per month).

Those in the meditation condition underwent a 56-day intervention that involved using the Muse system once a day. Daily sessions started with the syncing of the headband to the Muse app and the calibration of the headband technology. Next, participants undertook 1 of 10 guided introductory, instructional mindfulness meditation recordings available in the Muse app, each lasting 2 - 3 minutes (consumed in order for the first 10 days and then based on participant preference thereafter). These recordings provided instructions for how to sit for meditation and how to monitor, accept, or influence bodily sensations, breath, emotions, or thoughts. Next, participants used the immersive soundscape function for a 10-minute unguided meditation session with neurofeedback. In this neurofeedback session, different auditory cues within the Muse app indicated active, neutral, or calm brain states. Based on this auditory feedback, participants used the specific mindfulness meditation skills they learned in the instructional recording to pursue more calm brain states (indicated by the auditory feedback). At the end of these sessions, participants were provided with a report of the percentage of time spent in different brain states (active, neutral, or calm) according to the EEG data. All activities were undertaken within the free version of the Muse app, and all participants reported having completed all daily sessions.

Additionally, participants completed detailed questionnaire-style migraine headache diaries on the web each time they experienced migraine symptoms throughout the intervention period. These diaries queried information related to the onset (such as the time they noticed indicators of an oncoming migraine and migraine expectation—if they could predict the onset of migraine based on symptoms or triggers), nature (such as peak intensity, average intensity, and disability for the day), duration of pain (such as the time attack started and finished), participants' emotional state during these symptoms (such as stress, anxiety, irritability, happiness, sadness, anger, boredom, relaxation, and poor concentration), possible triggers (such as dietary, sleep, hormonal, environmental, physical, stress, and stress letdown), and any treatment techniques used to manage symptoms (such as resting in a quiet dark place, taking over-the-counter medicine, massaging the scalp, applying a cold compress, and drinking herbal tea).

For this study, participants who had completed the neurofeedback-based mindfulness meditation intervention with the Muse system were invited to undergo additional semistructured interviews regarding their experiences of this intervention. Interview data served as the basis of an interpretative phenomenological investigation [49] into how adults with migraine experienced an at-home neurofeedback-assisted mindfulness meditation practice. Potential participants were contacted by email, and no additional inclusion or exclusion criteria were applied. The first 10 individuals who agreed to participate were interviewed by the first author (TL). All current participants identified as White, and the majority were female participants (n=7). Ages ranged from 23 to 55 years, with a mean age of 32.6 (SD 9.59) years. With regard to employment status, 7 participants indicated that

they were students, homemakers, or volunteers, 1 noted they were unemployed or retired, and 2 chose not to answer. Though small, this sample size is consistent with the goals and purposes of interpretative phenomenological analysis [49].

Data Collection

Semistructured interviews were conducted with participants in December 2022. All interviews were conducted over Zoom (Zoom Video Communications), lasted between 20 and 70 minutes, and explored experiences of neurofeedback and mindfulness meditation with Muse. Participants were asked about the intervention's effects on their migraine symptoms, migraine frequency, coping mechanisms, quality of life, and activities of daily living. Participants were also asked about the influence of Muse on their meditation experience, their perceptions of the strengths and limitations of the system, and their intentions for future use of the Muse system and meditation techniques learned during the study. Interviews were audio recorded and subsequently transcribed by the first author (TL). Information on migraine and headache frequency was collected from participants before the intervention, with migraine frequency (monthly) ranging from 0.00 to 9.33, with an average of 3.09 (SD 2.89), and headache frequency (monthly) ranging from 0.33 to 11.67, with an average of 4.42 (SD 5.22). The time (months) between the end of the official intervention period and the interview ranged from 8.00 to 13.57 (mean 9.4, SD 4.54).

Data Analysis

Per the 6 steps of reflexive thematic analysis outlined by Braun and Clarke [50,51], the authors first familiarized themselves with the data. Data were then assessed for patterns (codes) of manifest and latent meanings using an inductive or bottom-up approach (though researchers' interpretations of the data were invariably influenced and nourished by their familiarity with existing literature). Codes were then assessed for recurring patterns and developed into a preliminary map of codes and themes, with themes representing a higher level of abstraction and codes fitting within one or more themes. This map was then refined in an iterative process of returning to the data and the literature and generating clear and precise theme descriptions as well as more abstract categories and more specific subthemes. The final step involved integrating these experiences into a cohesive structure that conveyed the relationship between categories, themes, and subthemes and the essence of the data as a whole.

Results

Overview

In sharing their experiences of neurofeedback-based mindfulness meditation using the Muse system, participants broadly spoke to 3 categories: the positive impact of mindfulness meditation with Muse on migraine experiences, enhanced well-being and improved quality of life resulting from the intervention, and the benefits and drawbacks of incorporating Muse technology into mindfulness meditation practices in the context of migraine treatment. In what follows, we elaborate on participants' experiences according to these 3 categories of information. Table 1 summarizes the key findings of the study, detailing categories, themes, and subthemes.

Table . A summary of key findings.

Category and theme		Subtheme	Values, n (%)
Positive impacts on migraine experience			
	Improved migraine management and prevention	Reduced frequency of migraine episodes	6 (60)
	Improved migraine management and prevention	Improved ability to prevent severe intensity migraine pain	9 (90)
	Improved migraine management and prevention	Better able to cope with acute migraine symptoms	9 (90)
	Transforming the experience of migraine	Reduced fear of migraine pain	5 (50)
	Transforming the experience of migraine	Feeling more empowered	7 (70)
	Transforming the experience of migraine	Developing a more constructive understanding of migraines	9 (90)
Enhanced well-being and improved quality of life			
	Improved psychoemotional well-being	—[a]	8 (80)
	Enhanced social relationships	—	7 (70)
	Establishment of healthier daily routines	—	6 (60)
	Enhanced appreciation for holistic health	—	9 (90)
	Fewer migraine-related disruptions to daily life	—	4 (40)
Perceived benefits and drawbacks of the portable EEG[b] device			
	Benefits of meditation with a portable EEG device	Session-tracking promoted adherence	9 (90)
	Benefits of meditation with a portable EEG device	Live EEG data were helpful in developing a meditation practice and tracking personal progress	10 (100)
	Drawbacks of the portable EEG device	Technological and instrumental challenges	10 (100)
	Drawbacks of the portable EEG device	Live auditory neurofeedback alerts were distracting	8 (80)
	Drawbacks of the portable EEG device	Perceived incongruencies between meditation experiences and EEG records were frustrating	8 (80)
	Drawbacks of the portable EEG device	The headband was uncomfortable during active migraine symptoms	5 (50)

[a]Not available.

[b]EEG: electroencephalogram.

The Positive Impact of Mindfulness Meditation With Muse on Migraine Experiences

In total, 9 of 10 participants reported significant improvements in their migraine experiences related to the neurofeedback-based mindfulness meditation intervention. These improvements included enhanced migraine management and prevention capacities as well as positive shifts in the experience of migraine.

Improved Migraine Management and Prevention

In total, 9 participants reported that neurofeedback-based mindfulness meditation with Muse improved migraine management and prevention by reducing the frequency of migraine episodes (6/10), enhancing their ability to prevent severe-intensity migraine pain (9/10), and providing effective strategies for coping with acute migraine pain (9/10). Speaking broadly to decreases in episode frequency and intensity, Participant 4 noted: “since I’ve done that practice [mindfulness meditation], I’ve had less frequent migraines ... [and] my migraines—they’re not as bad as they used to be.”

Participants largely attributed reduced migraine frequency and intensity to reductions in psychological stress and accompanying bodily tension through mindfulness meditation with Muse (9/10). Speaking of the relationship between stress and migraine attacks, Participant 9 explained that learning to calm the mind and relax the body on an ongoing basis served to reduce migraine frequency: "[The intervention] helped me, like, deal with outside stress ... like [I experienced] less stress in general." Many (7/10) also noted that the increased interoception (awareness of internal body signals) they developed as a result of this practice increased their awareness of early signs of an impending attack and improved their ability to identify possible triggers (including poor posture, certain repetitive motions, muscle tension in certain areas, prolonged immobility, stressful experiences, inadequate sleep, and dietary behaviors). In the words of Participant 3:

> *You can go by without even realizing where your pain is or what's going on in your body. So that was an opportunity for me to do that at least once a day, and just get that centering. And I think that helped me become more aware of my body in general, of some of the triggers that brought out a migraine.*

By avoiding such triggers or taking preventative action at the earliest signs of migraine, participants felt that they were able to effectively reduce the frequency of "full-blown" migraine attacks (characterized by moderate to severe intensity pain; 7/10). For example, Participant 8 described how becoming attuned to early warning signs of an impending migraine and prophylactically redirecting their attention while engaging in mindful breathing allowed them to prevent several migraine episodes: "I could ... stop my migraine without painkillers with diverting my attention ... I was like, take a deep breath, think about something else, and it was gone, and it never started that day." Participant 7 similarly explained how mindfulness meditation, in combination with the headache diary, allowed them to better identify and avoid migraine triggers, thus reducing the frequency of their occurrence: "I started to kind of notice the triggers more. Especially when I was doing those [migraine diaries] ... I would notice 'okay, this could be stressful, or this could give me a headache', and I would just stop."

These same factors (global reductions in psychological stress or bodily tension, increased awareness of specific triggers, and becoming more attuned to bodily signs of impending migraines) were also considered central to participants' sense of being better equipped to recognize early warning signs and initiate early behavioral responses that either prevented or reduced the intensity of the migraine attack. For example, by removing themselves from sources of agitation and initiating prophylactic pharmaceutical treatment, Participant 4 felt that they were able to prevent high-pain episodes and return to a state of wellness more quickly: "Before [the intervention] migraine would [mean I was] done the whole day ... I would just shut off from the world until it stopped. [Now], I take that break, and I focus on myself and ... then the pain reduces." Participant 9 similarly noted experiencing fewer high-intensity migraines since developing these skills: "the *severity* has been less."

In addition to reflecting on enhanced prevention efficacy, 9 participants also described using mindfulness meditation (with or without the Muse system) as a means of coping with acute migraine pain. Coping refers to voluntary thoughts and behaviors mobilized to manage internal and external stressful situations [4]. For example, Participant 7 described using mindfulness meditation with the Muse system outside of scheduled intervention sessions to cope with acute migraine pain: "it help[ed] with decreasing the pain ... when I meditated ... it sort of overtook that [migraine] pain." Participants proposed various theories about how mindfulness meditation was able to diminish migraine pain. In total, 7 participants attributed this ameliorative effect to enhanced attentional control and the ability to divert one's attention away from physical pain. For example, Participant 10 noted: "[For pain management], I would try to refocus just on my breath. So, I wasn't thinking about anything except for the breath." Participant 4 similarly described how the intervention taught them to divert their attention away from migraine pain to achieve relief: "I ... interrupt the pain or focus on something else [mantra and breath] and divert that pain ... [to] have some temporary relief."

Additionally, 5 participants noted developing the ability to separate themselves from embodied experiences of pain, known as psychological decoupling (mechanism of disengaging the physical aspects of pain from the emotional aspects of pain, leading to a reduced experience of distress through nonattachment [4]). Psychological decoupling leads to the ability to refocus attention, allowing individuals to experience lower pain through replaced focus, as Participant 1 noted: "letting go of ... [tensions] that are causing you pain ... removing yourself from, like, the experience of having pain ... a form of relaxing ... distancing myself from the stimulus of the pain."

Finally, 8 participants felt that the pain-reducing capacity of mindfulness meditation was tied to its ability to promote a state of profound psychological and physical relaxation. Participant 4 noted that the practice helped to "relax the brain" and reduce muscle tension in ways that diminished migraine pain. Participant 1 similarly explained that mindfulness meditation was about "letting go" of the many tensions "that are causing you pain."

As the participants developed and refined migraine prevention and pain management techniques throughout the intervention period, 6 participants reported reducing their use of pharmaceutical painkillers. Participant 5 noted that since the intervention, their "first jump isn't to the medication" anymore, further explaining that "I didn't take any medication because it didn't even occur to me to take it ... [during a migraine] I laid back down and ... I did my breathing [mindfulness meditation technique]." In addition, Participant 2 stated: "Once I got used to the meditation and kind of knew how I like to do it, and what kind of environment I like to be in, I would kind of reach for almost that instead of going to a medication."

Emboldened by alternative coping and pain management strategies, 3 participants spoke about delaying medication intake to see if they could manage the episode without pharmaceuticals. Participant 7 described: "if it's not as severe or I didn't think it

would be as severe, I would take less. Or I would try first [to manage the pain] without it."

Overall, the participants perceived the intervention as helpful for reducing migraine frequency and pain intensity through enhanced stress management, interoception, awareness of triggers, and earlier intervention. They also noted that neurofeedback-based mindfulness meditation benefited acute coping through enhanced attentional control and psychological decoupling. Thus, most participants felt that the intervention had improved their migraine symptoms and coping efficacy. As Participant 3 noted, learning new prevention and pain control strategies "helped me be able to cope with it [migraine], be able to understand it, and navigate it a little bit better than I used to."

Transforming the Experience of Migraine

In total, 9 participants described qualitative changes to their experiences and understandings of migraine that they associated with mindfulness meditation with Muse. As they learned to better predict, prevent, and cope with migraines throughout the intervention, these individuals described a reduced fear of pain (5/10), an increased sense of personal empowerment in living with migraines (7/10), and developing more constructive understandings of migraines (9/10). Living with an unpredictable, treatment-resistant, and debilitating chronic illness can be very stressful. As Estave et al [9] explained, part of the distress implicit in living with migraine and headache conditions is the anticipatory anxiety (AA) that comes with wondering when a migraine will occur, how painful and debilitating it might be, and whether it will respond to interventions.

Although none of the participants described meditation with Muse as having prevented all migraine attacks or fully eliminated migraine pain, many noted that developing even limited efficacy in preventing and treating migraines using mindfulness meditation reduced AA and increased feelings of self-efficacy in managing these conditions. In total, 5 participants described worrying less about the possibility of developing a migraine. For example, Participant 4 described how being better able to manage migraine pain through meditation practices helped dissipate a lot of the anxiety around possible episodes: "That dread went away ... I knew that I could try something different to divert it ... like 'oh, I'm going to get it [migraine pain] but it's not going to be that bad or I can do different things to mitigate it.'"

Participant 2 similarly described how feeling more capable of managing this condition reduced the sense of living with a wholly unpredictable and uncontrollable body: "[It is a] mind over body kind of thing, like I have the power to control my brain and so now that I am more attuned to it [the state of mind and body], I feel like I could kind of control how I was feeling ... I now had something [mindfulness meditation] that would help me feel better, that I knew helped me feel better."

Though all participants acknowledged that migraine symptoms would be an ongoing part of life, 7 participants noted that the sense of being able to effectively engage in some level of pain control and management reduced the fear around impending episodes. This sense of having even a modest degree of influence over the body and its symptoms not only reduced AA but also transformed individuals with migraine from passive survivors into active agents of their own well-being. Speaking about this developing sense of personal agency, Participant 7 stated, "it felt empowering—that I was somehow in control [of my migraines]."

In total, 9 participants described how becoming more attuned to embodied distress and environmental migraine triggers altered their perspective on migraine pain. As they grew more aware of the connections between migraine pain and a host of environmental, relational, and lifestyle stressors, these individuals came to understand migraine pain as an embodied sign that life was not in balance. Participant 3 noted, "[I started] seeing [migraine pain] less as an intrusion in my life, and more so as part of my life, or at least an expression of something going on in my life." In doing so, these individuals recast the body and its pain as informants and allies, capable of providing important insight into personal well-being and warning the individual about the need to slow down or re-establish balance. Continuing, Participant 3 explained: "I didn't feel that the meditations directly *reduced* my pain, but it affected how I *related* to that pain."

Enhanced Well-Being and Improved Quality of Life From the Intervention

In speaking about how mindfulness meditation with the Muse system influenced their daily lives, all participants described benefits beyond migraine prevention and pain management. Participants reported that mindfulness meditation with Muse benefited their psychological well-being, interpersonal relationships, work performance, and daily habits. In total, 8 participants noted general improvements in their psychological and emotional well-being as a result of mindfulness meditation, including reduced stress, a decrease in intrusive thoughts, an enhanced ability to achieve physical and mental relaxation, global improvements in mood, and greater energy, focus, and motivation throughout the day.

In total, 7 participants also reported that engaging in neurofeedback-based mindfulness meditation using the Muse system benefited their relationships and support systems. Participant 7 reported that participating in the intervention increased the visibility of prevention and coping efforts and occasioned more family conversations about migraine: "the kids became more aware of that [living with migraine] ... [that I] sometimes ... get sick." Participant 2 noted that the practice aided in emotional regulation, leading to fewer relationship difficulties: "I think definitely on the days where I did meditate ... thoughts are clearer ... [I could] get my, like, point across in discussions ... if I forgot to meditate ... I did feel like I would get more confrontational."

In total, 6 participants also felt that the intervention helped them establish healthier routines and sleep-wake cycles. For example, Participant 1 noted how getting up each day to complete the meditation exercise: "I would do the meditations every day ... first thing in the morning and so that ... helped build a better structure in my day that otherwise wouldn't have been there." Alternatively, participants who added mindfulness meditations to their evening routines felt that it helped them to relax and

prepare for sleep in ways that benefited sleep hygiene and quality. Participant 2 noted that it "helped me go to sleep ... brings my brain down to like the normal speed ... [makes] the end of the day ... feel like the end of the day ... and then sleep would come, like, in a more natural sense." Regardless of when participants meditated, the practice of taking 10 minutes each day to check in with the body, experience a quiet moment alone, and engage in a process of relaxation was deemed beneficial by all but 1 participant. Aside from any specific benefits to the migraine experience or one's cognitive, emotional, or social well-being, the mindfulness meditation intervention encouraged participants to spend a few moments engaging in "self-care" each day. As Participant 7 noted, the mindfulness meditation "provided a bit more different routine ... something to look forward to ... sometimes that's all you need to just kind of, like, relax."

Often, discussions of the intervention's benefits incorporated interrelated aspects of mind, body, and wellness. Participant 10, for instance, noted that the practice benefited his migraine symptoms, stress levels, and chronic muscle tension: "[Mindfulness meditation] would give me some relief overall, not just with migraines, but also with stress ... I have a lot of tension in my upper shoulders and neck area as well as my glutes, and ... everything relaxed more." Importantly, these diverse benefits were often said to have an interactive, additive effect, given the interconnectedness of mind, body, environment, and circumstances. In discussing such interactions, 9 participants spoke to a "positive domino effect," wherein proximal outcomes of checking in with and becoming more attuned to mind and body states lead to distal outcomes of positive lifestyle changes to improve mind and body states [4]. For example, 9 described how attending to the state of their minds and bodies during mindfulness meditation with live biofeedback led to sobering realizations about routine stress experiences and the inability to separate mind and body. Participant 9 expressed how they noticed "how stressed I was when I would approach the meditation ... I think, like, just being more cognizant of like how my body was feeling [during the meditation] ... in response to my mind was really huge." Such realizations prompted numerous lifestyle changes intended to eliminate or reduce chronic stressors, including reducing media consumption, stepping back from stressful activities, and seeking out restful activities in the evenings. Participant 7 noted, "I think [mindfulness meditation] really helped with kind of controlling the environment that might actually contribute to [migraine]." Here, meditation draws awareness to stress states and spurs practical life changes that subsequently benefit migraine symptoms by reducing daily stress and exposure to triggers. In such cases, mindfulness meditation with the Muse system helped individuals with migraine to appreciate the interpenetration of mind, body, and experience and spurred the pursuit of a healthier lifestyle.

Participants also described how an increased ability to prevent and manage migraine pain reduced disruptions to everyday life, allowing them to perform better at work and fulfill commitments in their personal lives. For instance, 4 participants noted that increased awareness of migraine triggers enabled them to optimize their work schedules and avoid taxing experiences throughout the day, thereby reducing absences and increasing performance. Participant 7, for example, described undertaking more strenuous work tasks at the beginning of the week and reducing responsibilities as the week wore on to avoid triggering weekend migraines. Fewer disruptions to activities of daily living meant that participants not only felt more in control of daily life but also experienced less worry, frustration, and guilt and thus reduced their ongoing exposure to stress-related migraines. As Participant 5 noted, a reduction in the frequency of migraine episodes led to fewer missed days at work: "Normally I would probably have ... two to three pretty bad ones that I would actually have to miss work for ... and I've only missed one day of work for migraine [since beginning the intervention]."

In this sense, mindfulness meditation helped to disrupt a negative loop, wherein the activity limitations of chronic pain increased everyday stress, which subsequently increased migraine frequency. Speaking about how enhanced pain management allowed them to complete activities of daily living and avoid the psychoemotional strain of unfinished projects and unmet obligations, Participant 7 noted: "meditating helped with decreasing the headache, then, of course, automatically, I would be better at concentrating and fulfilling that [work and life tasks]." Participant 5 similarly noted how mindfulness meditation left them feeling more driven and optimistic, which, in turn, allowed them to access social supports and leisure activities that increased their quality of life: "my motivation levels have increased significantly ... [I have] the energy to ... get through some stuff [after-work activities] ... that is a visible change from before [the intervention]." Here, we see how enhanced pain prevention and management benefited daily quality of life in ways that reduced global stress and daily disruptions, reducing exposure to migraine triggers. In short, throughout the course of the intervention, pragmatic coping skills, personal insights, and lifestyle changes interacted in dynamic ways to enhance the quality of life of participants.

In addition, neurofeedback-based mindfulness meditation not only improved migraine experiences for the majority of participants but also benefited the quality of life for individuals with migraine. These dual benefits were not independent but rather interacted in complex ways to benefit participants. Where meditation helped with pain control, it facilitated activities that increased the quality of life. Where quality of life improved, reduced stressors and experiences of migraine-related guilt and shame were thought to help prevent the onset of agitation-related migraines. A notable exception here was Participant 6, who reported no benefits from the intervention. In discussing this outcome with the interviewer, Participant 6 attributed the lack of therapeutic benefit to the "random" nature of their migraines, noting that daily hassles, psychological overwhelm, and embodied agitation were not related to the onset, severity, or duration of their migraines. They were convinced that mindfulness-based interventions would only be effective for stress-based migraines and described entering into the study without any expectation of positive benefit. We return to the significance of this case in the discussion. In what follows, we consider how participants understood the role of Muse technology in these positive outcomes.

Perceived Benefits and Drawbacks of Incorporating Muse Technology in Mindfulness Meditation in the Context of Migraine Treatment

Participants reported the benefits and drawbacks of incorporating live EEG feedback via Muse into their mindfulness meditation sessions. Participants largely spoke to the benefits of 2 Muse features. First, all except Participant 6 found the session-tracking feature beneficial for motivating adherence. Participant 1 noted, "the thing I really liked about [Muse™] was that ... you got an objective recording that you did the thing." Participants found seeing the record of completed exercises within the Muse app to be rewarding, sort of like a "a place to put the check mark" or an "objective recording that you did the thing" (Participant 1). Second, all participants found the live EEG data helpful for developing their meditation practice and tracking progress over time, such as how often and how long they meditated. For example, Participant 3 explained how the data on their mental activity provided objective documentation of a practice that can be difficult to monitor:

> *I think it's easier to deny ... or pretend that I'm not in a moment of frenetic [mental] activity or thinking [without neurofeedback]. I can just tell my mind to be quiet and then think that I'm quiet whereas the Muse™ neurofeedback—it's tracking something very different, not what I'm saying to myself, but my actual brain waves ... it provided a different perspective on my being while I was meditating. I thought that was really helpful.*

The EEG data offered valuable insights into their capacity to attain a meditative state, insights that could not necessarily be obtained through interoception alone. Participant 4 echoed this sentiment, finding the live EEG data helpful for making meditation practice more tangible and in so doing, easier and more enjoyable to learn: "[The Muse™ EEG data] helped improve the experience because you could understand what happened at those certain times [when the mind was more active], and you could work to correct it, make it better, or do what you need to do to maybe limit that issue." Without this neurofeedback, participants felt they would struggle to notice fluctuations in brain activity and track their progress over time.

Participants also reported negative aspects of meditation with the Muse device. These included technological and connectivity issues (eg, intermittent interruptions to the Bluetooth connection or inability to successfully pair the Muse device with the smartphone app), distraction and frustration related to EEG outputs, and headband discomfort. Technological and instrumental challenges were reported by all participants. Such issues were noted to be distracting and frustrating. Participant 5, who received a replacement band, explained, "when technology doesn't work it does hinder your ability to fully focus and enjoy the process." Connectivity issues not only detracted from the mindfulness meditation sessions but also threatened to dissuade consumer engagement altogether. As Participant 2 noted, it "takes time out of ... the meditation."

Interestingly, while all participants reported that the summative EEG feedback was helpful for monitoring their progress across sessions, 8 participants found the live auditory neurofeedback alerts distracting, specifically, the bird chirping sounds indicating calmness and the storm sounds signaling heightened mental activity. These auditory cues, provided by the Muse device, were reported to be counterproductive to the users' ability to maintain focus during meditation. They described negative feedback as particularly problematic, prompting frustration with one's practice and further unsettling the mind. The emphasis on auditory rewards and punishments was also broadly criticized by 6 participants for contributing to the "gamification" of meditation in a way that negatively altered the practice experience. Participant 1 noted, "often the feedback was negative towards the experience ... when it was positive it was more so positive for the wrong reason ... almost like a gamification process and not so much, like, adding to the quality of the meditation." For these reasons, 8 of the 10 participants described learning to tune out auditory feedback. Participant 2 explained:

> *I would try to almost chase the birds, which in turn caused more storms to come ... it was kind of like a negative feedback loop where I wanted the birds, but I was getting the storms, so I'd try hard to get the birds, but I'd get more storms ... [in time] I was able to ... let all that go ... if I heard birds, that was great. If I heard storms, cool.*

Participant 3 similarly noted, "I know that part of the practice is not to judge where your mind is but just to accept and witness where it is ... sometimes I can accept where I'm at, sometimes I'm like, 'No, I want to be calmer!'"

In total, 8 participants also reported that incongruencies between their perception of sessions and the information reflected in the EEG data bred feelings of frustration or disappointment. Participant 3 explained, "I was getting lots of storm noises, and not very many birds, and I was like, 'what is going on here?' ... the feedback was irritating in the sense that what I thought, or ... was expecting wasn't actually happening." Here again, participants reported learning to let go of negative emotions associated with this discrepancy and began to accept that their minds might be more active than they thought.

Finally, 5 participants found the Muse headband to be uncomfortable during active migraine symptoms. As Participant 4 noted, the added pressure of the band was a barrier to using the band during migraines: "that was difficult, because I know you need this, the data from the monitoring device, but when you have a migraine, that's difficult to put something on your head. You don't want to."

Despite these critiques, all participants reported the ongoing use of mindfulness meditation techniques acquired during the intervention to manage their migraine disorders. Of the 10 participants, 7 expressed intentions to persist with mindfulness meditation using the Muse device. For these individuals, the benefits of neurofeedback outweighed any frustrations related to connectivity issues or other device limitations. They found the Muse device instrumental in assessing their progress over time. Moreover, each of these 7 participants expressed a desire to continue learning new meditation techniques and incorporate

the mindfulness meditation practices acquired in the study into their daily routines.

Discussion

Principal Findings

In this study, we explored participants' experiences of an 8-week neurofeedback-based mindfulness meditation intervention using the Muse device to manage migraine. The intervention aimed to understand whether neurofeedback-based mindfulness meditation could alleviate migraine symptoms and improve quality of life. Our findings indicate that the intervention was perceived as beneficial to most participants, leading to improvements in migraine experiences, including decreased migraine severity and frequency, improved coping and prevention skills, and overall improved quality of life. This included cognitive and emotional benefits, enhanced relationships, increased work performance, and the formation of healthier daily habits. At times, migraine and quality of life benefits were interconnected in complex, mutually supportive ways. For example, where reduced migraine severity led to fewer work absences, professional stress and guilt diminished. This net reduction in stress and other negative emotions was seen to help prevent intense migraine symptoms, compounding the benefits of the intervention.

In total, 9 of 10 participants also felt that neurofeedback-based mindfulness meditation with Muse improved their ability to manage migraine symptoms and prevent high-intensity attacks through (1) enhanced attentional control; (2) improved awareness of thoughts, bodily sensations, and migraine triggers; (3) developing the ability to engage in psychological decoupling (mechanism of disengaging the physical aspects of pain from the emotional aspects of pain, leading to a reduced experience of distress through nonattachment [4]); and (4) an enhanced ability to achieve physical and mental relaxation. Such changes point to perceptions of reduced migraine-related disability as a result of the neurofeedback-based mindfulness meditation intervention.

While our study was the first to use at-home neurofeedback-based mindfulness meditation training, our findings support previous research regarding the use of mindfulness meditation to treat migraine and other chronic pain conditions, revealing that alternative treatments for migraine can be beneficial for migraine pain and overall quality of life. Previous studies on mindfulness meditation note similar improvements to overall well-being as the current research, including improved management of pain [24], better sleep [52], enhanced cognitive function, including attention and motivation [53], and improved emotional well-being, lowering stress and tension [22]. The processes by which mindfulness meditation was believed to improve migraine experiences were also aligned with past research, with participants noting the importance of learning to disengage and view pain differently [54], increasing body awareness [5], enhancing personal agency [24], and reducing stress [55].

The study highlights the importance of fostering enhanced self-efficacy for individuals with migraine. For those living with chronic, unpredictable, and debilitating health conditions, the sense of one's body being "out of control" often creates immense stress and tribulation [56-58]. As participants in our study noted, the sense of hopelessness and helplessness that can result from feeling powerless to predict, prevent, or manage physical pain and incapacity diminishes the quality of life and contributes to pain-related fear and migraine dread. Where those living with chronic illness can develop some sense of self-efficacy in understanding, predicting, or influencing extraordinary bodies, they foster a more constructive and optimistic relationship to migraines and a more empowered sense of self [57]. As past researchers have noted, mindfulness meditation interventions allow individuals with migraine to recognize warning signs of migraine and make decisions in their own treatment [5,6].

In addition to concrete shifts in pain severity, symptom frequency, mood, cognitive performance, and disability, participants also spoke to a more qualitative shift in the meaning and experience of migraine resulting from the intervention. By reframing migraine pain from a meaningless source of distress to a sign of overwhelm and the need for self-care and an indication that the person might need to make changes to everyday life, the illness experience is imbued with meaning and saved from radical antagonism and senselessness. Participants were able to construe painful bodies as attentive, caring bodies that bear witness to challenging life circumstances and provide clues about personal well-being. What emerges in these stories is the figure of the "able (hu)man" (sic)—who takes initiative, recognizes their own power, and actualizes their ability to intervene and persevere in their own life [59]. Such processes of narrative reconstruction and identity work to symbolically rescue those living with chronic pain and illness from tragedy and meaningless distress, reinfusing the migraine experience with hope and significance [59-63].

Current findings suggest that the Muse device had an overall positive impact on participants' experiences of the mindfulness meditation intervention. The primary benefits of this device were that it provided structure and accountability to the mindfulness meditation practices, keeping participants on track by providing daily data on the number of days they had meditated. Another benefit was the objective recording of their EEG data, showing the quality of their mindfulness meditation sessions. This was approached with positive attitudes, as it provided the reality rather than personal impressions of their sessions. This motivated participants to persist in the intervention, leading to participants striving for a less active mind during future mindfulness meditations. In addition, participants perceived drawbacks from the Muse technology, including connectivity issues, frustration with the feedback system, and concerns of the accuracy of the EEG data. There are improvements that could be made with this technology in order for participants to feel confident about using the Muse during their meditation sessions. However, the majority of participants listed the desire to continue mindfulness meditation with Muse in the future.

The study participants noted multiple benefits and drawbacks of the Muse technology, where the positive outcomes reported suggest that neurofeedback-based mindfulness meditation with

Muse technology could be a beneficial treatment tool for some individuals with migraine. The 1 divergent experience (Participant 6, who reported no benefits from the intervention and attributed their lack of success to the fact that their migraines were not stress-related) suggests the importance of understanding the causal ontologies affirmed by specific individuals with migraine to support the identification of best candidates. For example, those who do not consider particular triggers (such as stress) to be relevant to their migraine experiences are less likely to adhere to behavioral treatment modalities that target such triggers [64,65]. At the same time, it is well-established that beliefs about treatment effectiveness affect treatment outcomes [66]. Given these findings, greater attention to how endorsement of the "stress" hypothesis and beliefs about intervention effectiveness impact neurofeedback-based mindfulness meditation use, adherence, and outcomes among individuals with migraine is warranted.

The burden of living with migraine often results in individuals with migraine receiving pharmaceutical treatments, which are limited in a number of ways. Pharmaceutical treatments can lead to a reliance on medications and medication-overuse headaches [2]. In addition, pharmaceutical treatments should not be used by individuals living with stomach problems and who are pregnant or breastfeeding [2]. These limitations exhibit why alternative treatments, such as neurofeedback-based mindfulness meditations, should be available for individuals with migraine. Our study supports the growing body of research demonstrating the benefits of mindfulness meditation, such as improved management of chronic pain, emotional well-being, cognitive functioning, and overall perception [20,22,53,67,68]. These improvements have been found in quantitative research on alternative treatments of migraine, resulting in decreased migraine pain and disability and helping individuals recognize early warning signs of migraine [4,69]. This study expands on these findings from a qualitative perspective, revealing the importance of the lived experiences of individuals with migraine. This study reveals the importance of agency for individuals with migraine, as having a sense of control over their chronic disease allowed them to separate themselves from their migraine.

Limitations and Future Research

Several methodological limitations are worth noting. First, the original efficacy study excluded participants who regularly used preventative medication and who already practiced meditation (prior to the study). It is unclear if participants used other evidence-based migraine treatments (eg, botulinum toxin), and if so, to what extent. Second, a migraine diary was used to collect data on migraine frequency and symptoms. There is some evidence that a migraine diary alone can improve migraine symptoms and coping by making individuals with migraine more aware of their triggers [60]. Thus, reported improvements in migraine within this study cannot be attributed solely to the combined neurofeedback and mindfulness meditation intervention. Third, our sample size was limited and notably lacking in ethnic diversity. Finally, participants were interviewed at different times, ranging from a month to over a year after the original efficacy study. Results may be impacted by memory bias or the propensity to recall memories that are more congruent with current emotional states [70]. Interim factors like continued or discontinued use of the intervention, changes in migraine condition, and external influences (eg, lifestyle changes and medication use) may have also biased participants' perceptions of the intervention.

To our knowledge, this is the first study to examine a self-administered neurofeedback and mindfulness meditation intervention for migraine. Future research is needed to validate the effectiveness of this treatment protocol, control for potential confounds, and optimize the intervention. Follow-up studies with larger and more diverse participant groups would be beneficial for commenting on the generalizability of our findings and investigating how individual differences (symptoms, daily activities, and personal characteristics) might impact experiences of neurofeedback-based mindfulness meditation interventions for individuals with migraines. Longitudinal studies are needed to explore the effects of this intervention over time. Finally, the limitations of the Muse system noted by participants highlight the value of considering user input and perspectives. Future studies should explore how different user settings might benefit experiences and adherence rates and how to best reduce technological difficulties and related user frustrations. For example, future studies might consider whether the ability to omit (mute) distracting auditory cues enhances user experiences or increases intervention adherence. Biofeedback output could also be improved to make it more suitable for individuals with sensory disorders (eg, vibration instead of auditory cues). Moreover, the Muse system could address technical issues that cause difficulties in calibrating the device for participants and enhance the electrodes to ensure that they function more effectively. Continued exploration of user expectations and experiences is crucial to better understand the acceptability and feasibility of these mobile health tools and design quality consumer-grade migraine products that meet the needs and health objectives of diverse migraine experiences.

Conclusions

Notably, as the first study to evaluate the experiences of individuals with migraine in an at-home, neurofeedback-based mindfulness meditation intervention, this investigation adds to our understanding of nonpharmaceutical migraine treatment. The skills learned by participants in this intervention led to the perception of improved migraine symptoms and improvements in quality of life. This perception was brought on by an increased sense of agency, leading to a narrative shift toward a body that provides useful early warning signs and valuable insights into daily life and a self that is able to interpret and influence embodied distress. While changes in the severity and frequency of migraine pain as a result of the intervention are evident to greater or lesser degrees, this increased sense of agency also led to a higher sense of control over one's migraine, which can result in positive outcomes for coping with this disease. As the individual was transformed from a state of helplessness and hopelessness to one of increased agency and optimism, these experiences led to a profound shift in their global experience of migraine disorder. In addition, this type of treatment for migraine is safe and effective with few to no negative side effects, as the Muse device and mindfulness meditation have minimal negative implications. Consequently, this treatment should be considered on its own for individuals who are unable

to take pharmaceutical treatments for migraine. Additionally, this treatment should be considered alongside medication in order to learn the valuable coping and prevention techniques acquired in this neurofeedback-based mindfulness meditation intervention. Ideally, this would lead to individuals with migraine putting more reliance on mindfulness meditation for the treatment of migraine and reduce their medication intake. Ultimately, this study revealed that neurofeedback-based mindfulness meditation can be a valuable intervention for migraine, providing possibilities beyond pharmaceutical treatments.

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Authors' Contributions

TL, JG, FG, and MM contributed to the design and planning of the study. TL and JG contributed to the analysis and interpretation of the data. TL drafted the manuscript, and all authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AA: anticipatory anxiety
EEG: electroencephalogram

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