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COMMENT

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New opportunities for the early detection and treatment of cognitive decline: adherence challenges and the promise of smart and person-centered technologies

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Abstract

Early detection of age-related cognitive decline has transformative potential to advance the scientific understanding of cognitive impairments and possible treatments by identifying relevant participants for clinical trials. Furthermore, early detection is also key to early intervention once effective treatments have been developed. Novel approaches to the early detection of cognitive decline, for example through assessments administered via mobile apps, may require frequent home testing which can present adherence challenges. And, once decline has been detected, treatment might require frequent engagement with behavioral and/or lifestyle interventions (e.g., cognitive training), which present their own challenges with respect to adherence. We discuss state-of-the-art approaches to the early detection and treatment of cognitive decline, adherence challenges associated with these approaches, and the promise of smart and person-centered technologies to tackle adherence challenges. Specifically, we highlight prior and ongoing work conducted as part of the *Adherence Promotion with Person-centered Technology* (APPT) project, and how completed work will contribute to the design and development of a just-in-time, tailored, smart reminder system that infers participants' contexts and motivations, and how ongoing work might build toward a reminder system that incorporates dynamic machine learning algorithms capable of predicting and preventing adherence lapses before they happen. APPT activities and findings will have implications not just for cognitive assessment and training, but for technology-mediated adherence-support systems to facilitate physical exercise, nutrition, medication management, telehealth, and social connectivity, with the potential to broadly improve the engagement, health, and well-being of older adults.

Keywords Cognitive training, Alzheimer's disease and related dementias, Adherence

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Background

Population aging, coupled with age-related declines in cognition, represents an unprecedented challenge for the United States and the world. In the United States, the number of older adults (ages 65+) will dramatically increase from around 54 million in 2019 to 95 million in 2050 [1, 2], with individuals 85 years of age or older representing the fastest growing segment of the population. While aging comes with normative changes in cognition that may interfere with the performance of everyday tasks, unfortunately, these challenges are exacerbated in those experiencing non-normative cognitive declines [3–7]. The lifetime risk of developing dementia after age 65 was estimated to be 11% for men and 19% for women in the Framingham study [8], with more recent lifetime estimates for Alzheimer's disease in other longitudinal studies ranging from 25–35% for those 65+years old [9]. Currently, dementia is the seventh leading cause of death [10]. Worldwide, fifty-five million people are currently diagnosed with it—a number which is likely to underrepresent its actual prevalence [10, 11]. As the population ages, the number of people experiencing dementia is expected to triple by 2050, and associated costs are projected to rise from $1 trillion in 2018 to $2 trillion by 2030 [12]. Addressing normative and non-normative age-related changes to cognition is a vitally important goal that has substantial implications for the health, wellbeing, and independence of individuals and their families, but also has larger societal implications associated with the potential to reduce resources needed to support large numbers of individuals experiencing significant cognitive loss.

Cognitive assessment and adherence challenges

Traditional approaches to cognitive assessment

The early detection of cognitive decline, including decline related to Alzheimer's disease and related dementias (ADRD), is a crucial goal for many reasons, and is recognized as an unmet need and important aim in the *National Plan to Address Alzheimer's Disease* [13]. Early detection has transformative potential to advance our scientific understanding of cognitive impairments and potential treatments. Successful methods for detecting early decline have the potential to advance our understanding of interventions capable of slowing or reversing decline and their mechanisms of action by providing critical information relevant to the participant selection and recruitment process of clinical trials. Early detection can benefit efficacy studies by identifying potential participants who are at risk for cognitive decline within the study window. In addition, depending on the targeted mechanism, trials examining the effect of cognitive intervention might benefit from intervening early, at a point when prevention of substantial decline might still be possible, instead of focusing on reversing significant declines after they have already occurred. Further, in longitudinal cognitive aging studies, sensitive measures of early decline could help link declines to important lifestyle risk factors, providing crucial information to inform recommendations to middle-aged and older adults regarding the prevention of cognitive problems.

From the perspective of the aging adult, early detection is also associated with several potential benefits. For example, early detection of decline might prompt a physician visit and lifestyle changes associated with preserved cognitive functioning (e.g., changes to diet, increased physical activity, implementation of efforts to reduce hypertension). Evidence of decline can motivate the adoption of lifestyle changes or treatments at a point in time when they are potentially most effective. Early detection can also inform long-term care planning decisions. As function deteriorates, individuals may lose the ability to make their own healthcare decisions, and early detection of cognitive decline allows these decisions to be made in advance of substantial cognitive impairment. Other decisions would also benefit from early knowledge of pending dementia, including decisions related to where to live and with whom to live. Early detection can also help a family to better understand behavioral changes and avoid conflicts.

Unfortunately, accurately characterizing changes in cognition at the individual level represents a major challenge. The traditional approach has been to administer neuropsychological tests periodically over the course of many years. Infrequent testing means that declines may not be noticed until they begin to seriously impact functional ability and hence independence. This approach is also complicated by issues of measurement quality as it does not account for the fact that performance on cognitive tests is influenced by multiple processes including true cognitive decline, the effect of repeated exposure to the same test that can mask decline (practice effects), and state and contextual variables that transiently increase or decrease performance. Previous research has demonstrated that within-person variability from day-to-day on the performance of standard cognitive measures can be similar in magnitude to cross-sectional age differences of between 15 to 25 years [14]. This variability complicates interpretation of performance changes between two isolated assessments separated by time. Neuroimaging approaches to predicting cognitive decline and dementia are promising [15, 16], but can be expensive and difficult to administer.

New alternatives for cognitive assessment

Burst measurement designs that assess cognition many times over a short time period (bursts), with longer periods of time between each burst, have been proposed as more sensitive alternatives. These methods allow for the estimation of both age/intervention effects and practice effects independently, and produce measures of cognitive ability that are relatively uncontaminated by within-person variability [17–19]. Instead of testing that might take place at the office of a healthcare professional, valid and reliable burst measurement assessments can be self-administered at home through mobile technology, allowing for more frequent remote monitoring of cognitive health [20]. The ability to self-administer computerized assessments (e.g., [21]) is an appealing one, both because it encourages the long-term monitoring of cognitive status and is a safe and convenient workaround in a COVID-endemic world. This represents a major opportunity for advancement in the ability to detect meaningful changes in cognition.

Despite the promise, burst measurement designs introduce additional challenges that need to be understood and addressed. A significant challenge of this and other measurement designs (e.g., ecological momentary assessment) is adherence [22]. An individual may need to engage in assessments over the course of months, or even years, before cognitive decline is detected. Unfortunately, there is ample reason to suspect that long-term adherence will be poor based on the related literatures, for example medication, exercise, and cognitive training adherence studies [23, 24]. Even for brief two-week cognitive assessment studies, and within a relatively young and healthy participant sample pre-screened for the ability to adhere to a cognitive assessment protocols, 15% of assessments can be missed [20]. In the context of short ecological momentary assessment studies measuring health behaviors such as smoking, adherence rates can be as low as 55% [25], and for a brief 6-day study, depending on the adherence measure, 21% to 27% of assessments were missed [26]). Few studies can speak to adherence to home-based cognitive assessment protocols over many months or longer [27, 28], but accumulated evidence indicates that this will present a significant adherence challenge.

Cognitive training and adherence challenges

Once cognitive decline is detected, it would be ideal to intervene as early as possible to delay the rapid decline of cognition. Although controversial, a popular approach to prevent or reverse decline that has gained the interest of scientists and the public alike is computer-based cognitive training. Adherence is crucial to understanding the efficacy of cognitive training in the context of clinical trials. Furthermore, should cognitive training prove to be efficacious, adherence will also be crucial to home-based cognitive training in order for individuals to gain their benefits. Even if cognitive training is ultimately found to be ineffective, understanding adherence in this context can provide valuable insight into how to predict and prevent adherence failures for other technology-based interventions aimed at improving the health, wellbeing, and quality of life of older people.

Like many other treatment domains, beneficial interventions to improve cognition are not anticipated to have a major impact unless older adults fully engage with them. This was seen in the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) randomized controlled trial; participants who adhered less to reasoning training demonstrated smaller training benefits [29]. For memory training, cognitive benefits have also been found to be lower for less adherent individuals [30]. Anticipated adherence problems are consistent with the high attrition and low adherence rates of many home-based, technology-mediated cognitive training studies. Non-adherence impairs the ability of researchers to determine the efficacy of cognitive training. Owen et al. [31] conducted a six-week online study in which participants were asked to practice cognitive tasks designed to improve reasoning, memory, planning, visuospatial skills, and attention three times a week. Of 52,617 participants who were initially enrolled, only 11,430 completed both pre- and post-assessments and at least two full training sessions during the six-week period. Hardy et al. [32] also conducted a large, online, randomized controlled trial that evaluated a longer cognitive training protocol (10 weeks). Like Owen et al. [31], just a little over half of the participants completed the study. In a recent 6-month online study of cognitive training, out of 2,557 older adults who were randomly assigned to receive reasoning training, only 863 remained at the 6-month follow-up session [33]. Boot et al. [34] used a slightly longer training program that was twelve weeks in length. Hand-held digital games were assigned to target perceptual and cognitive abilities. For the intervention of interest participants only played, on average, 22 h of the 60 h of training requested. Although a number of technology-based cognitive interventions have demonstrated some promise with respect to improving perceptual and cognitive abilities (e.g. [35–37],), the ability of these interventions to impact the well-being of older adults at risk for age-related cognitive decline is likely to be minimal unless older adults are willing and able to engage in them.

State-of-the-art adherence promotion strategies

The adherence challenges affecting cognitive assessment and training also extend to other digital health interventions, including interventions utilizing mobile health apps for medication and fitness tracking. One common challenge is that patients may not have the necessary technology proficiency or may not be comfortable using technologies associated with digital health interventions. This is especially true for older adults. Another challenge is that digital health interventions often require a significant behavioral change on the part of patients. Despite these challenges, there are several strategies that have been used to promote adherence in these contexts, including providing as-needed support and education to help patients learn how to use associated technologies [38], using incentives or rewards to encourage adherence [39–41], and tailoring interventions to meet the needs and preferences of individuals [42]. A recent study by Trenorden et al. [38] recruited 7 older adults to complete pre-operative computerized cognitive training exercises and then 12 weeks of post-operative cognitive training. They found that regular supervised sessions were effective in reducing frustration and achieving high levels of adherence. However, this approach may not be scalable with available human resources. While financial incentives and rewards have been used in promoting adherence to physical exercise, there are no clear guidelines regarding the amount of incentives that would facilitate long-term positive habit formation [40]. A systematic review and meta-analysis published in 2013 found that financial incentives increased short-term exercise session attendance up to 6 months [41]. The impact of financial incentives in promoting cognitive assessment and training has not been studied adequately.

Previous research on adherence promotion heavily relied on tailored messages [43]. Tailoring is an effective health communication strategy that recognizes the complexity of health decision making and behavior change. Research has found that messages created based on an assessment and understanding of individual differences are more engaging and persuasive than generic or one-size-fits-all health messages. Moreover, meta-analyses provide empirical evidence of the benefits of tailored versus non-tailored interventions across a wide variety of health outcomes including smoking cessation, physical activity, diet and nutrition, and binge drinking (e.g., [44]). Computer-tailored interventions are behavior change interventions that use powerful expert systems to automate the collection of personal information and enable theory-based tailoring on a wide variety of psychosocial factors. These systems use complex algorithms to customize messages or recommended actions from a content database – approaching a level of tailoring that, in the past, could only be achieved through interactions with experts or trained health care providers [45]. These types of systems, however, require individual assessments that can be onerous to participants and require significantly more development time given the multiple iterations of tailored messages that need to be developed. Our research has shown that this level of sophistication may not be necessary to enhance the persuasiveness of such systems. Instead, the challenge is how to raise the perceived personal relevance of the health message [46]. We believe that tailoring based on personal data collected ubiquitously in the background or through early queries about their preferences may be a crucial step in finding a more cost-effective and efficacious approach for tailoring, which in turn has been found to be an effective method for promoting behavior change.

Underpinning many of the tailoring and mobile-health approaches just discussed is the idea that consistently monitoring behavior allows interventions to be delivered only as needed. This "just-in-time" design takes a two-pronged approach to boosting adherence [47]. First, it maximizes potential effectiveness by only administering interventions when the user is detected to be most receptive to it *or* most vulnerable to lapsing from it. The flip side of this design is that it also minimizes unwanted, undesired, or unnecessary engagement. Receiving inappropriately timed interventions has been shown to backfire by negatively impacting intervention engagement (i.e., motivation) and intervention fatigue (i.e., "burn out") [47]. The second prong of just-in-time designs is the ability to adaptively tune the timing and type of intervention for the individual. Changes in context, status, or behavior can influence the effectiveness of a potential intervention. Passively and continuously monitoring behavior allows individuals to receive the right type of intervention at the right time. Just-in-time approaches can be fully automated in certain clinical contexts, thereby reducing the burden on both users to input data and health-care professionals to output recommendations [48]. Their broad applicability is such that they have been used in many domains, including physical activity [49], alcohol use [50], mental illness [51], smoking [52], and obesity [53], with the nature of the intervention ranging from simple prompts and cues to performance feedback and rewards to strategy guidance and adaptation of difficulty (where applicable). Just-in-time designs highlight the benefits of user-centric tailoring that are sensitive to changes in time, context, and behavior.

Adherence Promotion with Person-centered Technology (APPT) project

Introduction to the APPT project and rationales

Unless people adhere to home-based assessments and interventions targeting cognitive health, any benefits of these approaches will be lost. In light of poor adherence, the Adherence Promotion with Person-centered

Technology (APPT) project is set up to address the problem by developing a just-in-time AI reminder system to support homebased assessments and interventions, with the ultimate goal to promote early detection and treatment of age-related declines in cognition [54] (See Fig. 1 for the schematic of the AI reminder system data pipeline of APPT). Our just-in-time adaptive intervention for promoting adherence will be implemented as a smart reminder system with tailored messages. The APPT project goals are to 1) enhance adherence to cognitive intervention and assessment protocols, 2) improve understanding of barriers to long-term adherence, and 3) assist in the development of algorithms for predicting and preventing adherence failures. We aim to investigate these issues within samples of older adults with and without cognitive impairment. Specifically, two studies will test an adaptive, personalized, and integrated technology support system predicted to boost adherence to cognitive protocols over and above a simpler scheduling and reminder system.

These studies will provide valuable and generalizable insight into not only the benefits of adherence support, but also of individual difference factors that shape protocol adherence (e.g., attitudes, cognitive ability, health status, personality, technology proficiency). This information will inform the process of identifying individuals who would benefit from additional support and predicting and preventing extended adherence failures before they happen. Results will have important implications that extend far beyond cognitive health; the methods and mechanisms uncovered will have broad implications for technology-mediated assessment and intervention protocols to enhance health and well-being in general.

Early studies of the APPT project

To design, develop, and evaluate such a just-in-time smart reminder system in the APPT project, we have done substantial preliminary work using quantitative, computational, and qualitative approaches to (1) understand the motivations for older adults to participate in behavioral research [55]; (2) understand older adults' attitudes toward the use of mobile and wearable technologies that support adherence and assess cognition [56]; 3) understand factors that influence older adults' adoption and sustained adherence to cognitive interventions [57]; and (4) evaluate the feasibility of using both baseline individual difference and brain game interaction data to predict the overall, weekly, and daily adherence to the cognitive training with advanced analytic approaches [58, 59]. In the following, we briefly summarize a subset of completed studies in the APPT project in two themes.

Theme 1 (understanding motivations and barriers to engagement)

To get people to consistently engage and adhere to an intervention in the context of a clinical trial, it may be useful to know what motivates people to enter such trials initially. When adherence lags, these motivations might be reinvigorated through targeted, tailored messages to encourage reengagement. Our recent publication in *The Gerontologist* [55] provided an initial evaluation of motivation typologies of actual and potential research volunteers for cognitive research studies based on surveys administered to participants recruited from an existing registry of older people who agreed to be contacted for research. By analyzing survey responses, we identified four classes of older participants based on their reported motivations: brain health advocates, research helpers, fun seekers, and multiple motivation enthusiast. Further, motivations could be predicted by individual difference

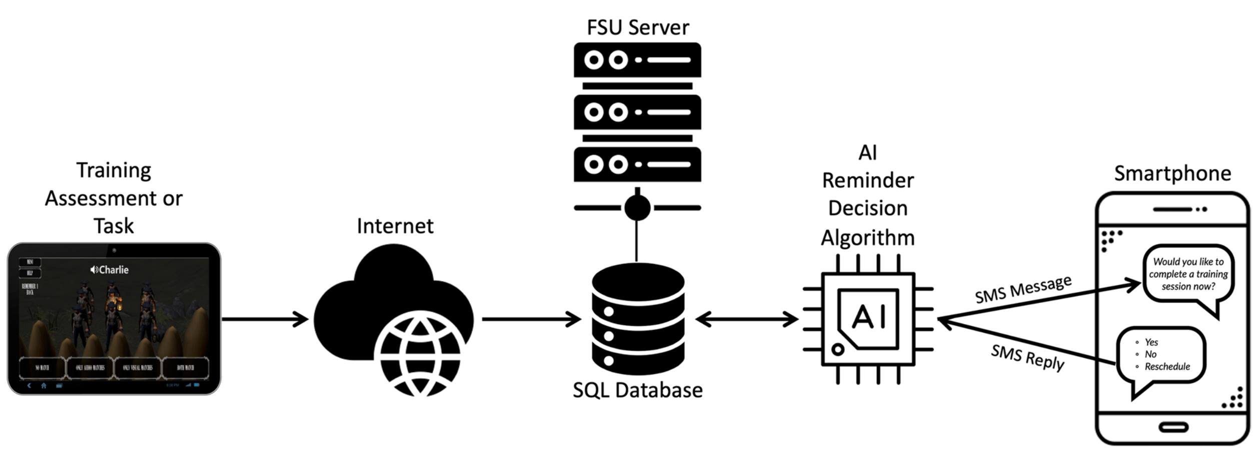

Fig. 1 Schematic of the AI reminder system data pipeline

characteristics, including employment status, age, perceived cognitive problems, and whether participants had engaged in previous research projects. In sum, these findings demonstrated that older adults have a variety of interests and motivations that may lead them to participate in research studies, and that motivations can be predicted to some degree in advance based on individual difference characteristics. This study was influential in shaping the motivations to be targeted in later APPT clinical trials of adherence support systems and validated the approach of tailored messaging.

Recently, we conducted a focus group study with 21 younger and 21 older adults to elucidate what factors might motivate individuals to adopt mobile versions of cognitive training and assessment protocols and what factors would sustain adherence to these protocols over time [57]. Recreational enjoyment and ease of engagement were prerequisites necessary to even considering the long-term use of cognitive protocols. Cognitive, social, and commitment factors were also important, but were subject to a complex cost–benefit analysis in which the comparative benefits or drawbacks of one factor could be down-weighted or up-weighted by that of another factor. Long-term engagement was also boosted by the customizability of settings and the inclusion of a dynamic reminder system. This study provided additional insight into the nature of the motivational messages to include as part of the APPT system and confirmed that tailored and adaptive approaches are desirable.

Finally, critical to the success of smart reminder systems is understanding and reducing attitudinal barriers to their use, as well as understanding older adults' attitudes toward the collection of data for the purposes of generating predictions about message content and timing and predicting future declines in cognition. Fowe and Boot [56] explored older adults' attitudes toward the use of wearable and mobile devices. Most relevant to the current paper, one scenario evaluated participants' attitudes toward a smartwatch that monitored the wearer's daily routine over time in order to provide reminders to engage in healthy behaviors, while a second scenario presented participants with a smartwatch that could predict future cognitive decline by tracking activity data. Contrary to stereotypes that older adults are technophobic and unwilling to adopt new technologies, participants rated hypothetical technologies as useful, were willing to recommend them to others, were interested in learning more about them and indicated willingness to adopt these technologies themselves. Results were encouraging with respect to older adults' acceptance of the technologies and approaches under development by the APPT project.

Theme 2 (predicting adherence through advanced analytic techniques)

The ultimate success of a smart adherence support system would entail being able to predict who is most likely to struggle with adherence and perhaps even predict when adherence failures might occur *before* they happen. This would allow for targeted and tailored adherence support. In our recently published study [58], we built multiple machine learning and deep learning models to predict participants' engagement using previously published data [60]. The dataset involved data collected from 118 community-dwelling older adults (*Mean age* = 72.6 years, *SD* = 5.54) who were asked to play a series of gamified neuropsychological tasks on tablets at home. In total, this dataset included records of 200,000 training interactions as well as a host of demographic, cognitive, attitudinal measures. We first used demographic and attitudinal data in logistic regression model to predict overall adherence with moderate accuracy (AUROC: 0.71). We then used weekly game play interaction data in Recurrent Neural Networks with Long-Short-Term-Memory (LSTM) and Gradient Recurrent Units to predict the following week's adherence throughout the 12-week training program with a high accuracy (AUROC: 0.84–0.86). We found that general self-efficacy, objective memory measures, and technology self-efficacy were most predictive of participants' overall adherence, while training time, number sessions played, and game outcomes were predictive of the following week's adherence.

In a parallel study using the same dataset by Harrell et al. [60], we built deep learning models to predict participants' daily adherence to cognitive training based on their past adherence patterns [59]. To do this, we leveraged the feature learning capabilities of deep neural networks, together with advanced signal processing techniques. We trained individualized, person-centered prediction models for each participant to capture their unique adherence behavior, rather than a single model for all participants; the final prediction accuracy was computed as the average accuracy across all the 118 participants. Our extensive empirical analyses corroborated the promise and potential of deep learning for adherence prediction, and produced highest mean F-scores (i.e., harmonic mean of precision and recall) of 75.5%, 75.5%, and 74.6% using CNN, LSTM, and CNN-LSTM models, respectively. Our efforts indicated that both individual difference characteristics and previous intervention interactions provide useful information for predicting adherence. These insights can provide cues for the just-in-time adherence support system of the APPT project to decide who and when to target with adherence support.

Planned studies of the APPT project

The initial pilot and development research has laid the groundwork for two large-scale clinical trials ($N = 190$ each) that will assess the impact of smart vs. standard reminder systems on older adults' adherence to home-based cognitive assessment and cognitive training. Community-dwelling older adults (ages 65+) will be asked to engage in either regular cognitive training via tablet (Study 1) or cognitive assessment via smartphone (Study 2) over the course of four months. Participants will be randomly assigned to receive text-message reminders during adherence lapses that are either tailored to their motivations (smart) or not tailored (standard), and are either timed appropriately to provide "just-in-time" support or not individually timed (standard). Adherence will automatically be logged and used to trigger text message alerts when adherence has failed in both conditions.

A key component of the smart reminder system is a consideration for the participants' likely context when the message is received. By context, we mean the tendency of people to form routines and habits. The best predictor of future behavior is past behavior. The best predictor of current context is likely past context. As a result, the current system uses participants' own histories of engagement with the cognitive assessment and training software to predict whether or not participants would be in an appropriate context to engage. For example, if a participant regularly engages in cognitive training every Tuesday at 2:00 pm, and then experiences an adherence lapse of several days, a "just-in-time" reminder might be delivered shortly before 2:00 pm the next Tuesday. The reminder system will learn participants' routines, and changes in those routines, through monitoring participants' engagement over time, giving more weight to more recent weeks to account for changes in routine.

At the end of these trials, two large datasets (over 350 participants in total) including detailed adherence and engagement data over several months, and dozens of individual difference measures spanning demographics, technology experience, attitudes, health status, and cognitive abilities will provide the raw materials for validating previous machine learning models discussed and developing even more sophisticated machine learning approaches to predict who is at greatest risk for adherence lapses and when adherence lapses are likely to occur.

Implications, future studies, and conclusions

The current research sets the stage for the ultimate goal of detecting and treating cognitive decline as early as possible, allowing for more efficient clinical trials, preserved independence of older adults, and reduced societal costs associated with Alzheimer's disease and related dementias. Uncovering successful methods for boosting adherence has been a challenge for decades, and novel approaches to understanding and supporting adherence are clearly necessary. Machine learning approaches developed thus far have provided some initial insight in that it appears possible to predict adherence challenges both at the level of the individual and also within the individual over time. An aspirational goal is to be able to predict and prevent adherence lapses before they happen by providing appropriately timed and individualized support. Although our approach has initially been developed in the context of adherence to home-based cognitive training, our hope is that generalizable lessons will be learned that might help support adherence in numerous other domains, including medications, diet, exercise, and other technology-based interventions. As technology continues to advance and more research is conducted on the most effective strategies for promoting adherence, it is likely that the use of digital health interventions will continue to grow and become increasingly effective in improving health outcomes.

Abbreviations

ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
ADL	Activities of Daily Living
ADRD	Alzheimer's disease and related dementias
APPT	Adherence Promotion with Person-centered Technology
IADL	Instrumental Activities of Daily Living
MCI	Mild cognitive impairment

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Availability of data and materials
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Declarations

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