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Leveraging technology to personalize cognitive enhancement methods in aging

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Abstract

As population aging advances at an increasing rate, efforts to help people maintain or improve cognitive function late in life are critical. Although some studies have shown promise, the question of whether cognitive training is an effective tool for improving general cognitive ability remains incompletely explored, and study results to date have been inconsistent. Most approaches to cognitive enhancement in older adults have taken a 'one size fits all' tack, as opposed to tailoring interventions to the specific needs of individuals. In this Perspective, we argue that modern technology has the potential to enable large-scale trials of public health interventions to enhance cognition in older adults in a personalized manner. Technology-based cognitive interventions that rely on closed-loop systems can be tailored to individuals in real time and have the potential for global testing, extending their reach to large and diverse populations of older adults. We propose that the future of cognitive enhancement in older adults will rely on harnessing new technologies in scientifically informed ways.

Population aging — the increasing percentage of older adults (OA) in a community — is poised to become one of the most significant social transformations of the twenty-first century, with implications for nearly all sectors of society[1]. Importantly, population aging will be accompanied by a proportionate increase in OA who will experience normal age-related cognitive impairments, as well as more severe cognitive decline[2,3]. Preventing or

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Author contributions

D. A. Z. and A. G. were responsible for conception and design, drafting, and substantial revisions. J. A. A., W.-Y. H., C. L. G., and P. E. W. were responsible for drafting and substantial revisions.

Competing interests

A. G. is co-founder, shareholder, BOD member, and advisor for Akili Interactive, a company that produces therapeutic video games. A. G. is shareholder and advisor for Neuroelectrics, a company that produces non-invasive brain stimulation devices and for Empatica, a company that produces biophysiological recording devices. The other authors declare no potential competing interests.

remediating cognitive decline in OA by as little as 1 year may delay the onset of nearly 10 million new cases of dementia[2]. Despite wide-spread enthusiasm for the development of cognitive enhancement approaches in this age group, numerous trials of cognitive training, dietary, and lifestyle interventions[4] have either failed to prevent cognitive decline or have had relatively modest effects. Further, several meta-analyses of cognitive training in younger populations[5–7] have failed to demonstrate far transfer of training gains (Box 1); however, other meta-analyses[8–10] and large-scale studies[11–13] that focused on OA suggest there is more potential in that group for broader gains from cognitive training. A common element in most of these studies is a one-size-fits-all approach that treats all participants in the same manner and ignores the vast degree of heterogeneity in older populations[14,15]. This is in contrast to other fields, such as geroscience, that have moved toward a precision-medicine model for combating age-related decline. The hallmarks of this approach are early and precise diagnosis and consideration of an individual's unique genetic, environmental, and lifestyle factors when selecting the most appropriate treatment[16]. A treatment plan can thus be tailored to the person, avoiding reliance on a typical trial-and-error approach.

Although some researchers have explored multimodal interventions to remediating cognitive decline[17], the precision-medicine model has not yet deeply penetrated the field of cognitive enhancement in aging[16]. For example, approaches to cognitive enhancement through the delivery of interactive experiences often fail to sufficiently engage OA with challenges, rewards, and stimuli that are appropriate for them — factors that are thought to be critical for maximizing neuroplasticity[18]. Modern technology, however, has the potential to transform this field by enabling cognitive interventions to be targeted to individuals who are most in need, as well as to those who will benefit most from a specific intervention. In addition, technology can offer dynamic tailoring of treatment parameters guided by an individual's state and condition in real time. Further, OA report being open to using new technologies for improving cognitive function, with a personalized approach seen as most desirable[19,20]. An important goal, therefore, is to bridge the gap between neuroscience and technology to develop and validate scientifically informed, technology-based interventions to explore the benefits of a precision-medicine model of cognitive enhancement for OA.

In this article, we will review progress in several technological domains that, from our perspective, hold great potential to transform the field of cognitive enhancement in OA: (1) developing new interventions that implement closed-loop systems to personalize delivery of plasticity-harnessing software, (2) advancing a precision-medicine model of cognitive enhancement through the identification of predictive biomarkers to deliver the most effective intervention to each person, (3) enabling remote, large-scale, real-world studies to validate promising results of laboratory-based studies of cognitive enhancement with smaller cohorts, and (4) expanding delivery of validated interventions to larger and more diverse populations. We will begin by reviewing the methodology of non-invasive, technology-based, closed-loop interventions and several examples of cognitive enhancement approaches that incorporate different instantiations of closed-loop systems in OA (Box 1).

Closing the loop on cognitive enhancement

We propose that many research studies on one-size-fits-all interventions have demonstrated relatively weak effects on cognition in OA because they are implemented through an open-loop system, such that the treatment (for example, a drug or training task) is either static or changes incrementally over time in a manner that does not reflect an individual's changing abilities in real time. This approach does not capitalize on the fact that, as a result of neuroplasticity, cognitive abilities are fluid over time. Thus, many cognitive interventions are either too easy or too difficult for an individual, particularly as their abilities improve over time. In contrast, a closed-loop system uses real-time, quantitative measurements that reflect a person's current state as the input arm of the loop (for example, performance, arousal, mood, and neural activity data) to guide real-time adjustments of stimuli, rewards, and difficulty of an intervention to close the loop (Fig. 1). Drawing on an extensive literature on signal-detection theory and Bayesian algorithms used for decades in psychophysics research[21], closed-loop interventions can be optimized to maintain a person's engagement with a task. As a person's performance improves over time, the task becomes more difficult; if the challenge is pushed too far and high-level performance is not sustained, then the task becomes easier. A closed-loop system thus maintains the challenge at a 'sweet spot,' maximizing fun and engagement by assuring that the intervention is never so hard that it is frustrating or so easy that is boring and thus achieving a maximal amount of engagement for driving neuroplasticity. A closed-loop system automatically personalizes the training regimen to an individual's data in real time and is critical for optimizing cognitive enhancement[18].

Emerging closed-loop cognitive enhancement technologies

In this section, we provide brief examples of emerging approaches to cognitive enhancement that rely on closed-loop designs and new technologies that show promise for transforming the field (see Fig. 2). Note that this selection does not include all approaches being pursued, but rather reflects specific domains in which the authors have the greatest level of experience and knowledge.

A closed-loop video game for enhancing cognitive control.

The enhancement of declining cognitive control abilities (for example, attention, working memory, and cognitive flexibility[18,22]) are of notable interest for OA because these abilities are particularly vulnerable to the effects of healthy aging and have a large impact on quality of life[23]. One of the first cognitive enhancement interventions to rely on a closed-loop system was the NeuroRacer intervention[24]. In a randomized controlled trial (RCT), it was demonstrated that healthy OA (60–85 years) who underwent 1 month of treatment with this custom-designed, closed-loop video game showed significant improvements in their cognitive control abilities, as assessed through untrained sustained-attention and working-memory tasks. These effects significantly exceeded those in both active- and no-contact-control groups[24], with observed improvements in multitasking performance on the game itself persisting 6 years later, without any booster training[25]. It has further been shown that other closed-loop neurotherapeutic approaches can lead to significant gains in cognitive control in both older humans[26–28] and aged rodents[26]. Validating closed-loop cognitive enhancement tools for older adults in randomized controlled trials to show meaningful cognitive gains and then advancing them as a regulated medical device will be especially important, given the number of products marketed as cognitive-aging and dementia treatments without scientific support.

Virtual reality for improving long-term memory.

In addition to cognitive control, declining long-term memory (LTM) affects diverse aspects of cognitive performance and results in an overall diminished quality of life for many healthy OA[29]. Chronic memory loss is typically first apparent as impairments in high-fidelity memory (that is, recalling distinct and specific information)[30], which is the most precise form of LTM. The progression of memory loss in aging is a cardinal sign of mild cognitive impairment (MCI[31]) and may foreshadow the onset of dementia[29]. High-fidelity memory depends on the flexible association of information that is remembered in distinct and detailed terms, and it depends on the hippocampal memory system[32,33]. Although practice and other mnemonic strategies have been shown to improve the ability to remember studied information[34], the goal of strengthening high-fidelity LTM mechanisms in OA with behavioral or pharmaceutical interventions has proven elusive. The animal literature has provided evidence that an exposure regimen of environmental enrichment can upregulate hippocampal functions[35,36], which in turn promotes better memory[37]. A similar approach to environmental enrichment in humans may generalize to improvements in high-fidelity LTM capabilities[38,39]. Yet applying these principles to humans, who have rich, detailed memories from a lifetime of experience, presents a unique challenge. Because upregulating hippocampal function is thought to result from encoding complex information into LTM[35,37], a principal challenge is presenting OA with information that is both novel and captivating enough to hold their deep engagement for an extended intervention; for example, an adaptive environment that is customized to each individual.

Modern technology now enables more elaborate and immersive sensory presentations and manipulation of a wider range of stimuli in cognitive interventions, thus leading to more engaging and personalized learning experiences. Studies have found that head-mounted-display virtual reality (HMD VR) drives greater engagement and increased performance relative to the same task presented on a flat-screen-monitor[40,41]. In terms of customizing the intervention environment, the use of HMD VR tools enables: (1) flexible control of the novelty of rich visual stimuli and game-play mechanics, which underpins development of the most intriguing learning experiences, and (2) increasing the engagement of participants in order to sustain their attentiveness and motivation for long, repeated training sessions that are necessary to achieve broader improvements in high-fidelity LTM. HMD VR makes realistic, three-dimensional perception possible and can synchronize a participant’s head movements (that is, the direction of their gaze) with walking motions to control ambulation and movement in the game, which together imbue greater ecological validity (that is, comparability to real-life experience) in the intervention sessions[42]. As such, OA can encounter a dynamic and personalized learning challenge (that is, environmental enrichment) with interventions using HMD VR. Further, several studies have shown that OA are often enthusiastic about using VR platforms, and research has shown that it is possible to design VR experiences that are accessible to OA[43]; therefore, getting OA to use VR at home is highly feasible[44].

To capitalize on these technological advantages, the Labyrinth intervention advances beyond flat-screen video games to stimulate learning in new spatial environments[45] by incorporating HMD VR and motion-capture sensors in a spatial wayfinding game[38]. Specifically, task performance in 3D VR uses binocular vision, which arises from a complex network of dorsal occipital areas and feeds a more intricate representation of the environment forward to enhance spatial-memory encoding[46]. The results from an intervention trial of Labyrinth showed that healthy OA increased their spatial wayfinding abilities in the game, but more importantly, these gains generalized to improved high-fidelity LTM performance on an unpracticed memory test[38]. Notably, post-training memory performance in OA who engaged with Labyrinth reached levels comparable to baseline high-fidelity LTM in younger adults.

Combining physical- and cognitive-challenge approaches.

Unlike the ambiguity surrounding the potential benefits of cognitive training for OA, the benefits of physical-fitness interventions have been well established in both healthy and cognitively impaired individuals[47–49]. Mechanistically, physical-fitness interventions have been shown to increase production of proteins such as BDNF, IGF-1, and VEGF[50,51], which modulate neurogenesis[52,53] and subsequently facilitate enhanced brain functions[54,55] through heightened brain network connectivity (discussed more below). Similarly, cognitive training has been shown to lead to increased neuronal plasticity at the cellular (for example, BDNF expression[56,57]) and network (for example, functional connectivity[24,58]) levels. New technologies, such as motion-capture sensors and VR, hold great promise for increasing engagement and enjoyment of physical-fitness training in OA[59].

Interestingly, results from animal studies have shown that linking physical and cognitive challenges can lead to synergistic enhancement of cognitive processes[60]. Although several studies[61,62] have sought to evaluate combined cognitive- and physical-training programs to enhance cognition in OA, the conclusions from these studies have been largely inconclusive, possibly owing to intervention delivery limitations. In some studies, participants alternated days devoted to each training modality and thus were not exposed to an integrated experience[61,62]. Other studies that attempted simultaneous physical and cognitive training inadvertently created an imbalanced training environment by failing to incorporate common goals that united the components[63,64]. Although these findings have not conclusively demonstrated synergistic effects, we still believe that such approaches are compelling options to maintain both cognitive and physical health in aging[65] and provide a time- and resource-efficient means of targeting multiple risk factors in OA[66]. Our perspective is that, to achieve synergistic effects, a combined cognitive and physical challenge should be delivered in an integrated manner without trade-offs across domains, and that this can be obtained by simultaneously engaging multiple closed-loop systems across areas to achieve a common outcome from a single intervention. This approach is currently being tested in clinical trials.

Meditation to bolster attention and reduce stress.

There is growing interest in using various forms of meditation as therapeutic interventions to enhance attention[67] and combat cognitive decline in OA[68]. In addition to leading to improvements in cognition[69], meditation and mindfulness practices have been studied as potential therapies for loneliness[70], depression[71], impulse control[72], and chronic pain management[73] in OA. Long-term meditation has been found to mitigate signs of brain aging[74,75] and improve well-being in OA[76]. At the same time, traditional forms of meditation can be challenging, intimidating, and expensive to learn because they require access to trained expert facilitators and/or in-person meetings over multiple months[77]. Moreover, these practices do not offer quantifiable metrics of success or performance feedback during the learning phases — factors that are important for maintaining engagement with an intervention[78]. Further, traditional meditation is difficult to personalize because it is not adaptive or tailored to individuals, making it overly challenging for some novices. Although recent studies have tested the delivery of website-accessible[79] and mobile[80] meditation programs, these online practices tend to duplicate the procedures of traditional meditation and consequently have faced similar hurdles to implementation. In addition, while meditation apps on mobile devices have become increasingly ubiquitous[81], studies to date have either failed to characterize their effects on cognition or have shown equivocal results[82].

An example of an approach to achieving a closed-loop digital meditation is MediTrain[83], which was designed with the goal of improving focused, sustained attention. This digital approach to meditation personalizes the experience to the real-time abilities of individuals, provides both punctuated and continuous feedback, and includes adaptivity that increases the challenge level as the user improves. Following several studies demonstrating a positive impact of MediTrain on attention in younger populations[83–85], a large-scale, fully remote trial of this digital intervention is being conducted in OA using a mobile RCT platform (Fig. 3). Interestingly, another modern, technology-enabled approach to meditation relies on neurofeedback from EEG signals recorded from a consumer device and has led to similar improvements in cognitive control[86]. These new technologically enabled types of meditation may open the door for personalization of treatments, with some forms (for example, neurofeedback versus performance-based feedback) working better for specific individuals.

Toward a precision-medicine approach to cognitive enhancement

The OA population is extremely heterogeneous[87]. Increasing age is associated with the risk of detrimental physiological or sensory changes, as well as increased risk of chronic diseases (for example, diabetes, cancer, heart disease, and cognitive impairment). At the same time, chronological age is not always a good predictor of functional capacity, with some individuals over the age of 80 continuing to work and travel, while other younger individuals are unable to. This variability in older populations is often overlooked when developing cognitive therapeutics, thus limiting the potential efficacy of interventions in some populations. Further, within trials of cognitive interventions, there is often pronounced variability in treatment responses that is ignored when reporting group averages, suggesting the need for additional personalization tactics. We propose that these differences represent meaningful heterogeneity, such that there is likely not a one-size-fits-all solution for cognitive enhancement in OA. In alignment with the broad concepts of precision medicine, we argue that, in the future, tailored treatment programs that target an individual's specific needs should be emphasized. A critical step to developing personalized interventions is identification of biomarkers that predict intervention success for a particular individual[88,89].

Some of the most promising personalization results come from studies that have used advanced neuroimaging methods to uncover neural factors that predict treatment success in an individual. Much of this work in OA has focused on metrics related to magnetic resonance imaging (MRI), spanning individual brain regions to large-scale brain-network properties[89,90]. Although much of the work using structural brain region predictors (for example, volume[91–93] and thickness[94]) has been largely inconclusive, more recently one common organizing principle of functional brain networks — modularity — has emerged as a potential unifying predictor of outcomes across a variety of interventions[90]. Modularity quantifies the separability of brain sub-networks into distinct communities, in which modular networks have many connections within and fewer connections between sub-networks, or 'modules.' OA with more modular brains show greater benefits from cognitive[95] and exercise interventions[96], and have faster learning rates during training[97], suggestive of a learning-related mechanism by which high modularity allows for larger training-related cognitive gains. Modularity may be a biomarker of cognitive plasticity that predicts treatment outcomes across interventions[90]. Although much of this work in OA has focused on MRI-related metrics, parallel findings in younger adults have identified electroencephalogram (EEG)-based markers that predict treatment outcomes[98]. Extending such EEG findings to OA will be an important next step as affordable, consumer-grade home EEG devices continue to increase in quality and ease of use, paving the way for at-home neural diagnostics that can be used to tailor intervention strategies or parameters to individuals.

Although it is clear that individual differences play an important role in intervention responsiveness[88,99], there are several lines of future work that will translate our understanding of these differences to developing personalized interventions. First, there is a need to better understand biomarkers of treatment outcomes. Understanding 'trait'-level predictors can identify what type of intervention is most beneficial for an individual. Further, understanding intra-individual variability can develop 'state'-level predictors that can be used in closed-loop adaptive algorithms and to identify when individuals will show training effects[89]. Second, it is likely that multiple biomarkers that span demographics, cognition, and neural profiles have interacting, and potentially additive, effects on predicting outcomes. Large-sample RCTs that incorporate machine learning will be critical in developing multimodal models that elucidate these predictive effects. Indeed, ongoing work is using an online citizen science approach to recruit tens of thousands of volunteers to validate and personalize cognitive enhancement technologies[100], and machine learning is now being used to optimize non-invasive brain-stimulation protocols for different individuals[101]. We anticipate a future of personalized digital therapeutics in which individuals are pre-assigned optimal training parameters, thus maximizing treatment outcomes for everyone.

Non-invasive brain stimulation to augment cognitive enhancement

An example of a technology-based, non-pharmacological strategy for enhancing cognition in aging that has benefited from a precision-medicine approach is non-invasive brain stimulation (NIBS). Of particular interest is the coupling of NIBS with cognitive challenges; the hypothesis is that targeted neural networks are selectively activated by task engagement and then further modulated by brain stimulation, resulting in synergistic neuro-enhancing effects that drive greater cognitive improvement[102]. This raises the possibility that NIBS could be used to augment any closed-loop, cognitive therapeutic approaches by enhancing the underlying neuroplasticity, thus leading to even greater cognitive enhancement. Two forms of NIBS methodologies are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). These techniques modulate neuronal transmembrane potentials by delivering weak electrical currents (tDCS[103] and tACS[104–106]), thereby altering plasticity in the stimulated brain regions[107,108].

Although the application of NIBS is generally thought to be a safe, non-pharmacological approach that has shown potential to counteract age-associated cognitive decline[109], crucial questions surrounding the heterogeneity of effects remain unaddressed. First, optimal stimulation protocols and regimes need to be established. The direction and magnitude of effects of NIBS are strongly influenced by the prevailing brain states in targeted regions at the time of stimulation[110,111]. Thus, the timing of the stimulation while a cognitive task is administered during the stimulation is critical. It is also possible that the brain's response to different stimulation protocols (for example, timing and context of stimulation) may be impacted by age-related changes in brain structure[112], metabolism[113], and neural plasticity[114]. Second, inter-individual variability exists in response to NIBS, with efficacy of NIBS being related to degree of education[115], genotype[116], pre-intervention performance[117], and the magnitude of the electric fields that reach the targeted brain area[118], which underscores the importance of individualizing stimulation parameters.

Further, given age-related decreases in brain volume[112] and broadening of cerebrospinal fluid space[119], which alters the conduction of current vectors[120], employing computational models that account for anatomical variables can help estimate the spread of NIBS-induced electric/magnetic fields in the brain and allow for individually personalized stimulation intensity. Similarly, studies have demonstrated that tACS effects are most prominent when the stimulation frequency is closest to an individual's endogenous peak oscillatory frequency[121], suggesting that an individualized stimulation frequency should be pre-determined for each participant[122]. In summary, an effective use of NIBS to induce cognitive enhancement in aging brains likely requires an integration of optimal stimulation protocols and individually tailored stimulation parameters to more precisely target the specific functional networks that underlie cognitive functions most in need of improvement.

Mobile technology to validate cognitive enhancement approaches

Testing hypotheses about the factors that predict or moderate treatment responses in the remarkably heterogenous OA population requires large and diverse cohort samples. Such large-scale studies are also needed to move the field beyond findings from relatively small studies towards the real-world validation of cognitive therapeutic technologies. While such data are critical to achieving the goal of a personalized approach to cognitive enhancement during aging, most large-scale RCTs rely on inherently costly, and often cumbersome, multisite ‘brick and mortar’ trials[123]. An emerging solution is to leverage modern, mobile technology (for example, the Internet, wireless mobile devices, and cloud-based analytical and storage servers) to facilitate the recruitment of larger, more diverse, representative cohorts into clinical trials while minimizing costs. The need for such a solution has been augmented by the COVID-19 pandemic, which has led to an even greater necessity for new, creative tools for improving public mental health in the setting of such unpredictable conditions.

New digital health technologies also hold promise for altering the landscape of how RCTs are conducted (Fig. 3). Indeed, it is now clear that mobile technology can be especially powerful in improving research-participant access, especially to those living in rural areas or members of minority ethnic groups, while simultaneously reducing the expense and time course of such trials[124]. Most of these research platforms have been designed to assist with enrolling participants, collecting data, and applying human resources for data interrogation, rather than complex study coordination. However, we believe that the next phase of this field will use technology for more than data collection, but also to make easily interpretable data more actionable for both researchers and participants. Indeed, there is an important value in developing technology not only to collect data, but also to accelerate the pace of research and enhance the security of data collected remotely (for example, through cloud-based analytics and storage). Large-scale, fully remote trials conducted in real-world settings (that is, people’s homes) are a crucial step in validating both existing and emerging cognitive enhancement technologies that to date have largely been studied in small, well-controlled laboratory settings that lack ecological validity.

Increasing access to cognitive enhancement technologies

Relevant to this discussion, more OA are embracing new technology every year. For example, smartphone adoption by all OA was 77% in 2020 (as opposed to 50% in 2014), including 62% of OA who are over 70 years old[125]. The clear trend is toward increased adoption of mobile technologies, making it important to study and refine digital interventions for enhancing cognition now, so they can reach as many OA as possible. Critically, the percentage of the population that owns a mobile device is equally distributed among white, Black, and Hispanic people[126–128]. Thus, fully remote trials of digital therapeutics have the potential to greatly increase the ability to disseminate these interventions at scale and to reach drastically more diverse study populations than would be expected from a trial that requires participants to come into a medical or research center. One step toward addressing this goal is making such tools easily accessible. This vision has been shared by numerous academic[129] and industry[130] initiatives (for example, Patient-Centered Outcomes Research Institute-funded Patient-Centered Clinical Outcomes Research Networks, the US National Institutes of Health Precision Medicine Initiative, and Apple’s Research Kit) that have championed the use of mobile technology to mitigate access-related barriers. Research has demonstrated that telemedicine and mobile approaches show comparable efficacy to in-person treatment[131], resulting in substantial interest in using mobile apps as an alternative care-delivery platform. Such digital approaches to cognitive enhancement have the potential for breaking down barriers to access, especially in under-served or hard-to-reach populations of OA[132].

The future of technology-based cognitive enhancement

We have reviewed several approaches in which technology can aid in the personalization of cognitive enhancement in aging, but other emerging technologies also offer exciting new avenues for innovation. For example, we imagine the creation and implementation of digital research platforms that would facilitate the rapid optimization of a given mobile intervention in near real time using a sequential multiple assignment randomized trial design while adapting the intervention parameters to each participant's specific needs[133], thus leading to true personalization of treatment. Elements such as art, music, story, challenge, and competition could be dynamically manipulated to maximize engagement and compliance to further personalize experiences. Key to such an approach will be collection of large amounts of data and the application of machine-learning and artificial-intelligence techniques to create robust and dynamic predictive models of the factors that moderate treatment responses at the individual level. There are a host of new accessible mobile technologies that can be leveraged to collect ecologically valid data as individualized baseline signatures and ongoing diagnostic monitoring of OA in the real-world and in real-time[134].

In addition to cognitive enhancement, technology is transforming the broader landscape of mental health and high-quality, personalized care for healthy OA who are living longer with each generation. Technologies that attempt to modify and support real-life behaviors have advanced at a tremendous pace in recent years. For example, several methods have been developed to combat loneliness, anxiety, and depression, which are common in OA[135]. Examples include online and mobile delivery of established clinical treatments, such as cognitive behavioral therapy[136]; VR paradigms for fostering greater feelings of connectedness and boosting mood[137]; artificial-intelligence-driven voice-activated technologies (for example, Alexa) that not only help with organization and access to news and media, but also increase connectedness through human–machine conversations[138]; and therapeutic robots in the form of appealing animals that help OA cope with anxiety and memory loss[136].

These technologies are exciting and add to the emerging ecosystem of methods that can be tailored to the specific needs of an individual. The impact of these therapeutic technologies could be augmented through combinatorial approaches (as discussed above) and by the incorporation of closed-loop systems (for example, a robotic companion that receives passive physiological signals from a wearable device and uses those data to guide its real-time engagement with its OA companion). It's clear that the future of aging will be impacted tremendously by harnessing new technologies in scientifically informed ways to enhance quality of life in old age.

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Box 1 |

A glossary of key terms

3D head-mounted display virtual reality (HMD VR):

Participants are visually and auditorily immersed in a virtual environment using HMD VR, in which they can easily discern the dimension of depth (3D) because imagery is presented via binocular, curved-field lenses mounted in the headset. A less effective illusion of depth perspective (2.5D) can be achieved on two-dimensional monitors via specialized graphics software. Participants do not experience an immersive environment with computer or tablet screens.

Closed-loop system:

A system (also called a feedback system) that adapts its output on the basis of real-time, quantitative measurements from the input arm. A closed-loop cognitive intervention might adapt the rewards and difficulty of a task on the basis of data reflecting elements of a person's current state (for example, performance metrics, autonomic responses, patterns of brain activity), thus tailoring the intervention to the individual in real-time.

Cognitive enhancement:

Cognition refers to the mental processes required to gain knowledge and achieve goals, including attention, memory, perception, decision making, language, and emotional regulation. Enhancement is a lasting increase in one or more of these abilities above a personal baseline, whether that is considered normal or impaired.

Cognitive intervention:

A non-pharmacological approach to enhancing cognition that is based on scientifically informed principles of neuroplasticity (that is, the ability of the brain to change).

High-fidelity long-term memory (LTM):

Recalling distinct and specific information for episodic, spatial, associative or temporal order details about a prior experience. High-fidelity LTM depends on the hippocampus.

Network modularity:

A graph theoretical approach to model functional networks in the brain. Modularity quantifies the extent to which a network is partitioned into sub-networks (also referred to as modules or communities). A network with high modularity has many connections within sub-networks and fewer connections between sub-networks.

Non-invasive brain stimulation (NIBS):

A set of technologies in which various patterns of electrical or magnetic stimulation are used to alter brain activity from the surface of the scalp without breaking the skin.

Precision medicine:

An approach that tailors medical treatments to the individual, rather than taking a one-size-fits-all approach. The most appropriate and optimal treatment parameters are selected based on genetic, environmental, and lifestyle factors that may predict treatment success for an individual. Sometimes referred to as 'personalized medicine.'

SMART design:

The sequential multiple assignment randomized trial (SMART) is a type of research study designed to allow the testing of multiple potential adaptive interventions while tailoring key variables.

Transfer:

The degree to which the learning of a new skill or task benefits an individual's performance on a different, unpracticed task. Transfer is sometimes referred to as generalization.

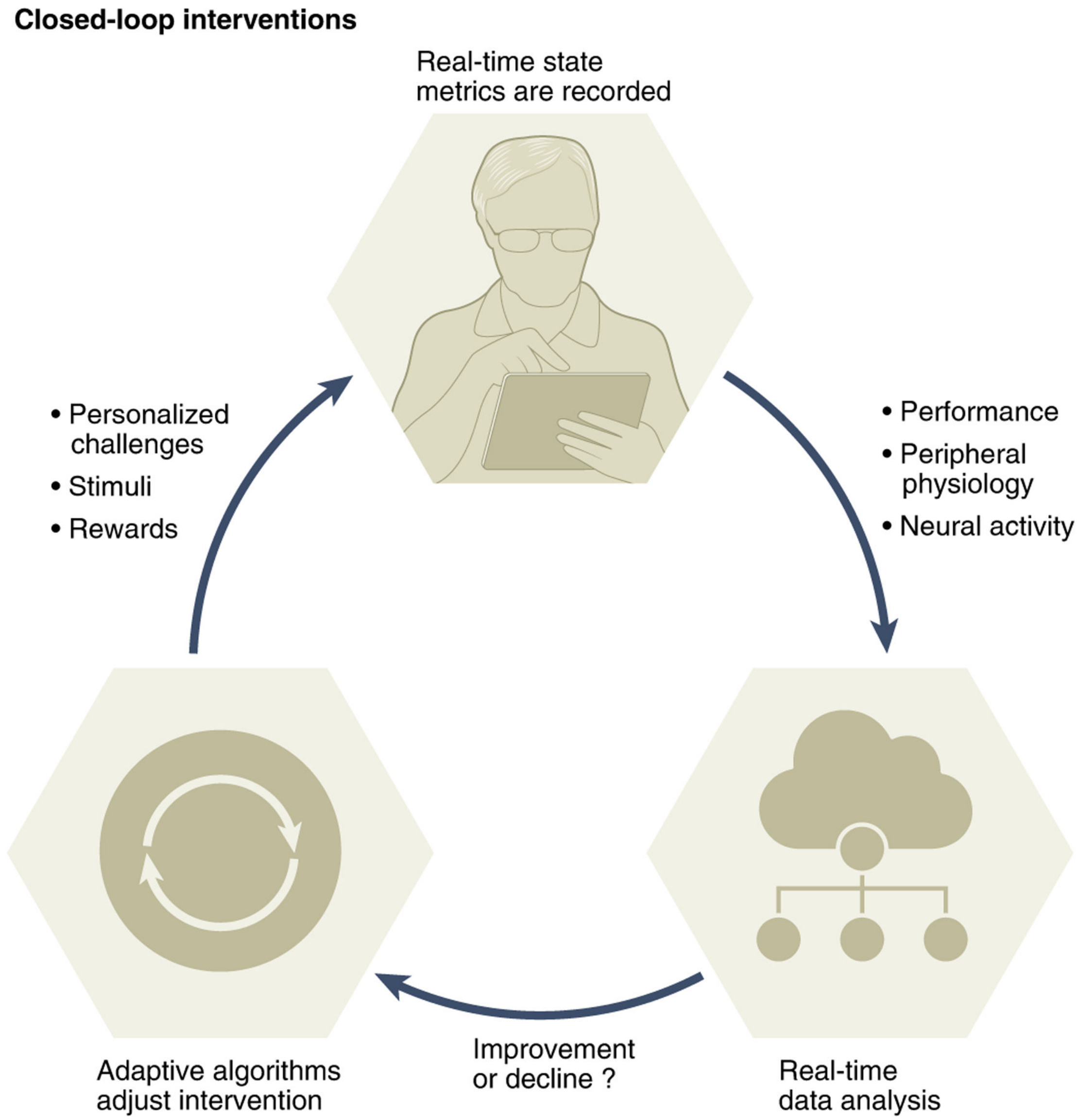

Fig. 1 |. Elements that define a closed-loop system.

As a participant interacts with a cognitive assessment or intervention, data are collected about the person's state (for example, task performance, arousal, neural activity). These data are analyzed in real time, either on the participant's device or using advanced cloud-based analytics to characterize the person's state in that moment, and adaptive algorithms are used to adjust the challenge, rewards, and stimuli, thus tailoring the intervention to the individual's current state.

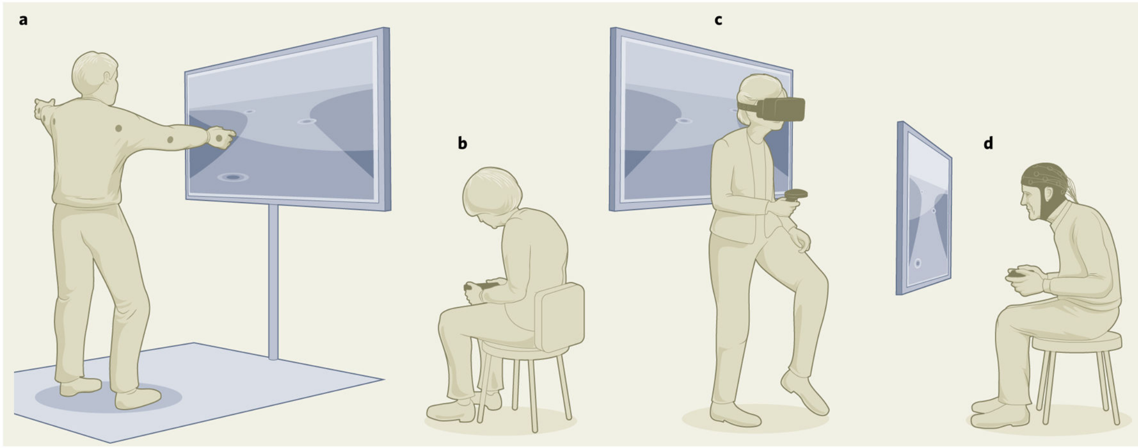

Fig. 2 |. Examples of technologies for personalized cognitive enhancement in aging.

a, Combining fitness and cognitive challenges in a meaningful way can lead to synergistic effects of an intervention. **b**, Digital forms of meditation make the practice more accessible to large, diverse populations. **c**, Head-mounted VR displays enable highly immersive environments that provide the context and engagement needed to bolster long-term memory functions. **d**, Neurostimulation applied in conjunction with a cognitive intervention can help accelerate learning and enhance gains in cognitive abilities.

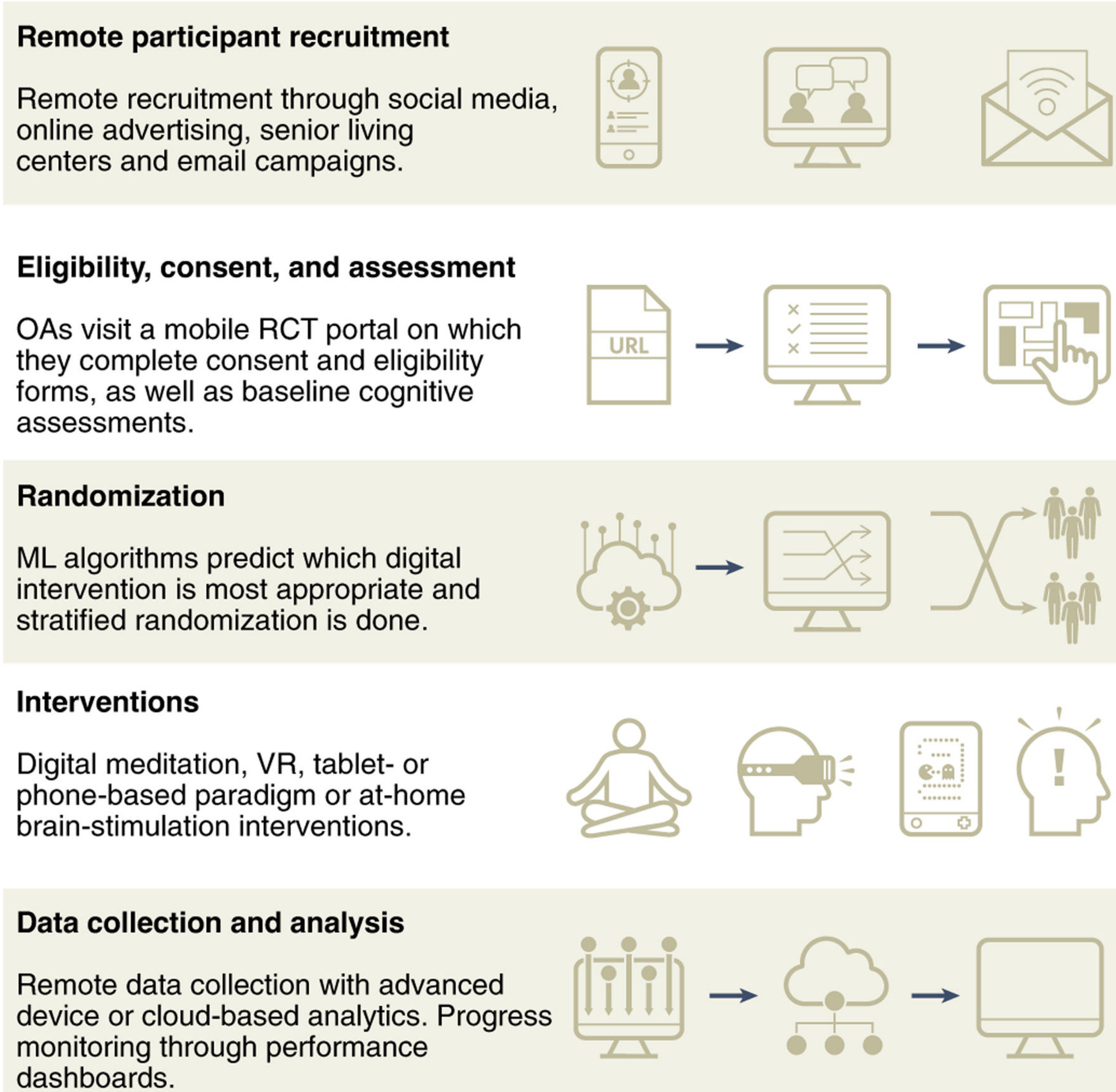

Fig. 3 |. Our vision for the future of mobile RCTs.

First, recruitment is conducted entirely remotely through social-media outreach, online advertisements, agreements with senior living centers, and direct mail campaigns. Next, OA are sent a link to visit a mobile RCT portal where they complete informed consent and eligibility forms on their computers or mobile devices. They then complete baseline cognitive assessments, demographic questionnaires, and surveys of real-life behaviors and conditions, and those data are input into machine-learning algorithms that predict which digital intervention is most appropriate for each person, and randomization is done in a stratified manner. Once assigned to an arm, OA complete the digital intervention at home while data are collected remotely. Finally, advanced device or cloud-based analytics allow for rapid analysis of results in real time, accelerating the pace of research and discovery. These results can then be interpreted by researchers or visualized and presented to the participants as a performance dashboard, enabling them to monitor their own progress.