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Review

Unifying framework for cognitive training interventions in brain aging

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ABSTRACT

Cognitive training is a promising tool for slowing or preventing cognitive decline in older adults at-risk for dementia. Its success, however, has been limited by a lack of evidence showing that it reliably causes broad training effects: improvements in cognition across a range of domains that lead to real-world benefits. Here, we propose a framework for enhancing the effect of cognitive training interventions in brain aging. The focus is on (A) developing cognitive training task paradigms that are informed by population-level cognitive characteristics and pathophysiology, and (B) personalizing how these sets are presented to participants during training via feedback loops that aim to optimize "mismatch" between participant capacity and training demands using both adaptation and random variability. In this way, cognitive training can better alter whole-brain topology in a manner that supports broad training effects in the context of brain aging.

1. Introduction

Identifying effective strategies to slow or prevent brain changes that accompany dementia-related diseases (i.e., "brain aging") or to compensate for these changes is essential for cognitive aging and dementia research. The progress, however, has been slow (Sikkes et al., 2021). A key obstacle has been an inadequate understanding of mechanisms of action among interventions that aim to slow cognitive decline (Jack Jr et al., 2018). Here, we aim to provide a framework for understanding the *mechanisms of action* by which cognitive training interventions could be used to address brain aging. Our overarching premise is that successful models need to comprehensively consider how neural mechanisms and intervention design can be leveraged and integrated to maximize real world benefits.

2. Broad training effects following cognitive training are elusive

Cognitive training describes a class of non-pharmacological interventions based on the idea that training processes at-risk for decline can lead to improvements in cognitive functioning in the real world. These approaches are typically built on well-established tasks from cognitive neuroscience and psychology. As such, these tasks have well-characterized cognitive and neural bases from decades of cognitive and, more recently, neuroimaging research. Extensive background research can therefore be leveraged to make inferences about mechanistic brain changes and their relationship to dementia pathology. However, the clinical utility of cognitive training has been limited by the relative narrowness of the training effects, and by methodological issues including insufficient sample sizes and variable control groups (for review, see (von Bastian et al., 2022)). For most cognitive tasks, training leads to reliable improvements in the trained task (trained effect, Fig. 1). In addition, the effects of training often transfer to cognitive tasks that have not been trained but rely on similar cognitive processes (i.e., near transfer effects (Kelly et al., 2014)). Comparatively rarer are training-related improvements in domains that are not directly related to the trained domain (i.e., far transfer effects (Sala et al., 2019)). Even isolated cases of far transfer, while encouraging, are of modest clinical significance. The ideal outcome of cognitive training intervention is to cause broad training effects in cognitive functioning more generally (Fig. 1), with associated improvements in everyday tasks in the real world. This goal, however, has been elusive, particularly in individuals at-risk for dementia (Basak et al., 2020b; Sala and Gobet, 2019; Sherman et al., 2020). To capitalize on the promise that cognitive training interventions hold for meaningful and mechanistically-interpretable improvements in cognitive functioning, it is imperative to develop frameworks for understanding and inducing broad training effects in individuals at-risk for dementia.

Despite the difficulty in reliably and robustly demonstrating broad

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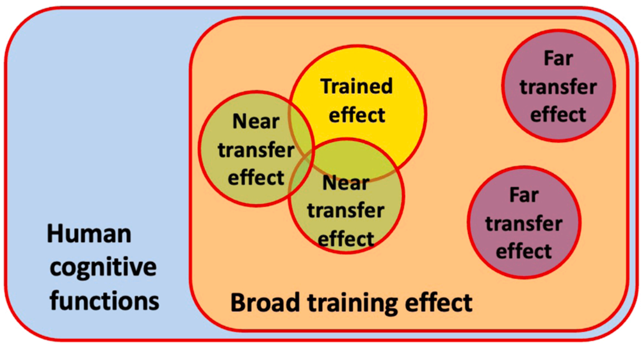

Fig. 1. Key concepts for understanding distinct types of effects from cognitive training. Cognitive training reliably leads to improvements in the trained task (i.e., trained effect), but to demonstrate clinical utility transfer of learning to untrained domains is necessary. Improvements only in domains with overlapping processes with the trained task are known as near transfer effects, while far transfer effects describe improvements in tasks that do not share processes. Broad training effect describes improvements to a broad range of cognitive functions, an outcome with maximal real-world benefits.

training effects following cognitive training, there are some reasons to be optimistic. While, some researchers (Sala and Gobet, 2019) have suggested that there is no evidence, particularly in younger adults, that cognitive training interventions can improve general cognitive ability (a latent factor explaining the shared variance across a range of cognitive tests that is important for broad training effects), and some studies have failed to find evidence of effects from cognitive training interventions in older adults (Kallio et al., 2018), other studies show positive findings (Gates and Sachdev, 2014; Lampit et al., 2015). Critically, meta-analyses of cognitive training studies in older adults and those at-risk for dementia (Hill et al., 2017; Zhang et al., 2019) suggest that training can result in both far transfer (Basak et al., 2020a; Harvey et al., 2018; Kelly et al., 2014; Mewborn et al., 2017) and improvements in clinical outcomes, including the ability to perform instrumental activities of daily living (Corbett et al., 2015), although findings vary even across meta-analyses (Bahar-Fuchs et al., 2019). Instrumental activities of daily living include tasks (e.g., shopping for groceries, managing medication, preparing and cooking food) that are fundamental to living independently, and improvements in these measures is suggestive that cognitive training can demonstrate broad training effects with clinical relevance.

Evidence from previous research provides an important foundation on which to improve cognitive training, and provides some clues as to which approaches are most successful. Working memory training is the most researched and, arguably, the most contentious (Harvey et al., 2018), with some studies showing no evidence of transfer (Guye and Von Bastian, 2017; Lampit et al., 2014) and others showing significant transfer effects (Mewborn et al., 2017). Speed of processing training is less common, but has shown promising effects (Chen et al., 2022; Edwards et al., 2017; Lin et al., 2016; Wolinsky et al., 2015). The dose-dependency of training effects is also unclear, with some studies showing a dose-response relationship (Corbett et al., 2015; Edwards et al., 2017), others suggesting at least 10 sessions are needed (Kelly et al., 2014), and one meta-analysis suggesting that 3 or fewer training sessions per week is better than more sessions (Lampit et al., 2014). Less ambiguous are the findings that adaptive (Kelly et al., 2014) training (training that changes based on individual performance) and multi-component (Nguyen et al., 2019) training (training more than one cognitive domain) are more effective than fixed and single component training, respectively. The durability of results also varies, with some studies showing no effects after 3 months (Zelinski et al., 2011), other suggesting that effects are maintained over time (Nguyen et al., 2019), and one study reporting a reduction in dementia risk at 10-year follow-up, although only in comparison to a no contact control group (Edwards et al., 2017). Overall, this research provides cautious optimism that cognitive training interventions have the potential to produce clinically meaningful broad training effects in older adults and those at-risk for dementia, and suggest that multi-component, adaptive, training programs are most effective. Few studies include measures that reflect broad training effects, including measures of everyday cognition and activities of daily living that reflect a clinically meaningful goal for interventions in older adults at-risk for dementia.

3. Existing inefficiencies in cognitive training programs for addressing brain aging

In spite of these promising findings, research on cognitive training programs to slow or prevent dementia has been relatively stagnant, and large-scale trials demonstrating clinically meaningful broad training effects are still lacking. We believe this is due to inefficiencies in the design of cognitive training, partly resulting from a lack of a clear mechanistic framework within which to develop and test cognitive training programs. Firstly, there are inefficiencies in the ways in which the challenge sets/training tasks (the combination of tasks, requirements, and stimuli) that make up cognitive training programs are designed for specific targets/populations. Most paradigms are built on well-established cognitive tasks, rather than reverse engineered starting with the overarching goal of causing broad training effects in older adults at-risk for dementia. Existing theories suggest that transfer of learning from trained to untrained domains (i.e., transfer) relies on improving component processes that are shared across domains. Namely, the idea is that the degree to which training affects untrained domains depends on the degree of overlapping component processes (Lovden et al., 2011). While there is some evidence for this theory (Dahlin et al., 2008), most cognitive training paradigms are still very narrow in terms of the cognitive processes they target, a feature that limits the degree of transfer (Sala and Gobet, 2019). Brain aging brings additional obstacles. When dementia pathology (e.g., amyloidosis, tauopathy, neurodegeneration) is present, broad training effects become even more challenging to demonstrate, likely because brain pathology interferes with the ability of the brain to adapt following training (i.e., show neuroplasticity) (Li et al., 2013; Müller-Schiffmann et al., 2015).

We argue that cognitive training paradigms can be improved if they are population-informed: designed to provide the most benefits for specific target populations. In our case, the primary goal is designing cognitive training tasks that maximize beneficial broad training effects in the context of brain aging. To accomplish this goal, cognitive training paradigms need to be informed by theories of brain aging that acknowledge cognitive and pathophysiological heterogeneity both within and across brain aging disorders. It is important to clarify that the idea that specific processes should be targeted by cognitive training based on target population characteristics is not new (Fissler et al., 2013). These approaches are predominantly aimed at improving specific processes that are at-risk, and we believe that they can be effective in cases with highly specific deficits, but are unlikely to result in broad training effects. In our approach, the primary goal is not to guide training programs *towards* cognitive processes that are at-risk, but *away from* neural processing that is unlikely to be amenable to intervention via plasticity due to disorder-specific pathology and neurodegeneration. We believe that cognitive training programs can be designed to induce broad training effects via various pathways, but that these pathways need to be relatively intact to allow long-term, large-scale changes in brain organization that are necessary for broad training effects.

The selection of appropriate challenge sets, however, is just the first step. There are also inefficiencies in the personalization of training paradigms — the mechanics by which training is delivered and changed in response to a trainee's performance. Learning theories indicate that learning requires an appropriately sized "mismatch" – a gap between the capacity of the brain and the requirements of the external task that the brain must adapt to in order to improve performance (Lovden et al., 2011). Learning is impaired if the task is ether too easy or too hard for the subject, a concept known as the Goldilocks effect (Seitz, 2018). This is particularly problematic in older adults at-risk for dementia (Beishon et al., 2021): cognitive impairments can make even simple tasks challenging, and individuals may need to start with pen and paper approaches before moving to computerized tasks. These computerized tasks also become more demanding in older adults due to reduced computer literacy that can lead to reduced adherence to computerized cognitive training (Turunen et al., 2019). As a person is expected to improve over the course of the training intervention, these "mismatch" theories indicate that task difficulty should increase in parallel with performance improvements (Hung and Seitz, 2014). This approach, which is widely used in training interventions, may not be well-suited to induce broad training effects. When executed well, adaptive procedures, such as "staircases", ensure that each subject will perform the task at a relatively fixed level of difficulty over the course of the intervention. While this may promote learning on the trained task, with extensive training, it usually lead to outcomes that are highly specific to the stimuli being trained (Li et al., 2013), or to the characteristics of the training procedure. Computational approaches have shown that increased specificity of learning occurs with higher task precision (Wenliang and Seitz, 2018). Research from perceptual learning has shown that the brain can adapt specific stages of a process to improve precise behavioral performance, for example, by improving discrimination of a specific axis or orientation in a specific part of the retina via isolated plasticity in the primary visual cortex (Seitz, 2018). In contrast, training where task difficultly is more variable leads to greater transfer effects (Hung and Seitz, 2014).

We believe that two related but distinct features of training: variability and novelty, are critical for broad plasticity (Li et al., 2013). Fissler et al. (2013) proposed an "overlapping variability framework", aimed at including both novelty and variability in targeted cognitive training interventions that they suggested would be able to overcome learning specificity, however, sensitive staircase designs are still most commonly used in cognitive training programs. These designs excel at maintaining a fixed level of task difficulty within a single task. Training with tasks focused on simply maximizing difficulty on a particular dimension, which is the norm in cognitive training, likely increases task-specific improvements, but also favors brain plasticity that is incompatible with broad training effects. Simply stated, when the training task can be solved by finding a specific solution it is effective and efficient for the brain to do just that. Thus, the goal of designing training mechanisms is to create a variable "mismatch" between a person's brain capacity and a range of cognitive training challenges that are representative of real-world requirements (Seitz, 2018), to induce neuroplasticity (Lovden et al., 2011) that leads to broad training effects by preventing focused, single-task solutions. This principle is the basis for many cognitive training programs (Fissler et al., 2013), but we believe that interpreting the mismatch in terms of broad training effects (i.e., measured using objective biomarkers) rather than within specific processes (i.e., measures of task performance) is critical for improving clinically meaningful cognitive training outcomes.

4. Benefits of population-informed and personalized training paradigms

We propose that advances in cognitive training interventions for older adults require a careful paradigm design consideration that is informed by an understanding of theories of learning as well as the overarching goal of improving broad cognitive functioning specifically in older adults at-risk for dementia (Seitz, 2018). This goal requires both a consideration of the behavioral cognitive training literature and of associated neural changes. Neuroimaging tools are essential here as they provide a window into the neurocognitive mechanisms involved in broad training effects from cognitive training, and can provide insights that inform future paradigm design. In particular, we suggest that the development of effective cognitive training interventions should critically rely upon understanding brain pathology and theories of brain aging in relation to cognitive resistance and resilience (Box 1), and the cognitive and pathophysiological heterogeneity within and across brain aging disorders. Building on brain imaging, cognitive training, and dementia prevention research by us and others, we will outline a framework for maximizing the effects of cognitive training interventions. The focus is on both on the task design and approach to adapting task challenges during training. In order to be population-informed, our argument is that the development of cognitive training paradigms should be based on an understanding of specific brain network architecture that is related to the functional training goals but also critically takes into account knowledge from population data informing different profiles of pathophysiology, as well as the neurocognitive status of the population being trained. In the context of brain aging, this population-informed strategy suggests certain task paradigms may be particularly relevant: tasks target brain networks underlying cognitive, sensory, and affective processes that are known to contribute to cognitive decline with aging but that may be spared from pathophysiology. In regard to personalization, intervention procedures should be tailored to trainees' current abilities and the training objective in a way that favors transfer over specificity. This emphasizes the importance of *within-individual dynamics* of adaptation that transpire over the course of a cognitive training intervention, and can be monitored using neural and physiological recordings that reflect adaptation capacity (Chen et al., 2020b). We believe that combining population-informed task designs based on facilitating broad training effects with personalization that maintains novelty and variability across the numerous cognitive domains targeting brain plasticity over prolonged periods will lead to significant improvements in broad cognitive function in older adults at-risk for dementia (Fig. 2). In the reminder of this review, we outline several concrete approaches toward achieving these goals.

5. Population-informed cognitive training design

Theories suggest that targeting domain-general processes and/or multiple domain-specific processes, is more likely to result in broader transfer (Dahlin et al., 2008; Maniglia and Seitz, 2018), due to a greater overlap between brain networks activated by training and those involved in a range of non-trained domains. In line with this, literature has generally suggested that multi-component cognitive training is especially beneficial (Deveau et al., 2015), but a detailed understanding of the specific components engaged during these training programs is often lacking, hindering progress towards a more precise mechanistic understanding of their benefits. Domains of cognitive function preferentially recruit different brain networks, and age and neurodegeneration affect the involvement of brain networks in selected cognitive domains (Li et al., 2015). Accordingly, stimulating brain networks involved in cognitive training paradigms requires an identification of the brain networks relevant to the cognitive components of interest and resistant to neurodegeneration in the target population.

The relative resistance of sensory processing to neurodegeneration can be incorporated into the design of task paradigms.

Efficiency of information processing, often measured via tests of processing speed and attention (PS/A), is fundamental for cognitive, social, physical, and affective function (Lin et al., 2013). Thus, this highly domain general process is a promising target for facilitating broad training effects. Dissociable subnetworks of neural connections with the frontal-striatal-parietal system are involved in supporting PS/A of different sensory stimuli (e.g., visual, auditory, or multisensory) (Amso and Scerif, 2015; Koelewijn et al., 2010). There are several advantages of targeting sensory-driven PS/A among groups at-risk for dementia: (A) PS/A is more plastic and flexible, so modifiable, than many higher level cognitive processes, especially in old age (Salthouse, 1996); (B) PS/A declines in general during typical aging (Lipnicki et al., 2017; Salthouse, 1996, 2010), which indicates room for improvement across at-risk groups; (C) sensory-related brain networks remain

Box 1
How does cognitive training affect cognitive resistance and resilience in the context of brain aging?.

Cognitive training approaches and frameworks, including the one presented here, need to be embedded within broader theories of brain aging and dementia before they can have maximum impact. Important to these theories is the idea that cognition can be protected, either via resistance to change (i.e., absence of neurodegeneration in the aging process) or via resilience (i.e., mechanisms that enable cognitive functioning even in the presence of pathology and damage) (Arenaza-Urquijo and Vemuri, 2020). In our framework, several steps may be influenced or influence brain-aging related factors (e.g., the preserved cognitive, sensory, and affective process for the top-down regulation, autonomic nervous system function, the reserve and plasticity of brain topology). Research to date has lacked clarity on whether proposed mechanisms of cognitive training act via improving resistance or resilience, partly due to a lack of explanation of whether training exploits naturally occurring mechanisms employed during normal cognitive aging or whether there are unique mechanisms involved. Answering these questions will help further validate the usefulness of the proposed cognitive training framework for preventing or slowing cognitive decline and dementia.

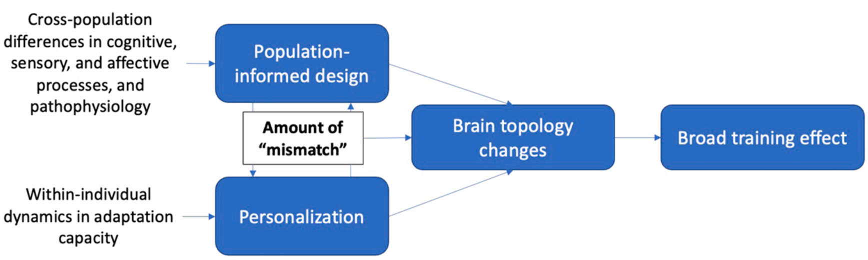

Fig. 2. Population-informed and personalized training paradigms for improved broad training effects in the context of brain aging. Cognitive training paradigms in the context of brain aging need to be developed based on the end goal of broadly improving cognitive functions. The selection of paradigms should take into account population-level differences known to impact the likelihood of broad training effects in older adults at risk for dementia. Additionally, to create prolonged and effective mismatches in cognitive resources needed for long lasting broad training effects, training must adapt to the trainees' performance in a personalized manner. Personalized and population-informed paradigms should aim to alter whole-brain topology that underlies the efficient neural processing needed for general behavioral performance.

relatively robust to dementia pathologies, which ensure the potential for plasticity during training (Braak et al., 2011); and (D) aging-related neural dedifferentiation leads to greater integration across multiple brain networks beyond sensory circuits for regulating sensory responses (Koen and Rugg, 2019); therefore training using sensory stimuli may stimulate “higher-level” networks more directly in older adults. Given these advantages, it is not surprising that speed of processing (SOP) training, focused on enhancing PS/A, is one of the most widely examined types of computerized cognitive training in aging populations (see e.g., ACTIVE (Ball et al., 2002; Rebok et al., 2014), IMPACT (Smith et al., 2009), IHAMS (Wolinsky et al., 2013), CogTE (Lin et al., 2016; Lin et al., 2020)). For example, in our previous CogTE study (Chen et al., 2020b; Lin et al., 2020), we revealed significantly better learning (i.e., near transfer effect), and greater activation of superior frontal gyrus, inferior frontal gyrus, and dorsal anterior cingulate cortex in PS/A tasks in a vision-based SOP training than an active control group; and the changes in learning and changes in brain activation were significantly positively correlated. While most studies have relied on vision-based SOP tasks, there is evidence that involving other senses, particularly audition, leads to additional benefits. In younger adults, cognitive training incorporating both visual and auditory stimuli with requirements for learning in both sensory modalities provides better training effects than unisensory training (Shams and Seitz, 2008). One hypothesis is that multisensory tasks involve a broader sets of brain mechanisms, extending the impact of the training (Pahor et al., 2021). For example, auditory-oriented SOP training seems to rely on different brain networks from visual-oriented SOP training (Amso and Scerif, 2015). Older adults maintain sufficient capacity for multisensory integration (Mishra and Gazzaley, 2013), and seem to benefit even more (i.e., greater increase in learning) than younger adults from multisensory training. Real world functioning relies on tasks that involve auditory (e.g., communicating via telephone) and visual (e.g., preparing meals) processes, and often benefits from integration between the two (e.g., during speech comprehension; Erber, 1975). While largely understudied, combining SOPs practicing visual, auditory, or audiovisual-integrated attention as a multisensory SOP package (i.e., mix-SOP) may target more processes that are important for real-world cognition, producing broad training effects to a greater degree. Overall, evidence indicates that training involving multiple senses improves outcomes (Shams and Seitz, 2008), and we speculate that this is due to the recruitment of a broader set of cognitive mechanisms.

5.1. Brain topology is critical for understanding broad training effect

A complementary strategy for developing better cognitive training interventions is to consider which brain changes are predictive of broad training effects. Several authors have outlined the importance of a clearer understanding of the neural mechanisms involved in improvements following cognitive training. Lovden et al. (2011) argued that it was critical to differentiate changes that resulted in alternations of functional supply – causing brain “plasticity” – from those that adapt existing functional supply – causing brain “flexibility”. More recently, von Bastian and colleagues proposed a related framework for differentiating changes in “capacity” (similar to Lovden's plasticity definition), from changes in “efficiency” (more akin to Lovden's “flexibility”), and argued that most evidence suggests that cognitive training works most often via changes in “efficiency”, i.e., how the brain uses its existing resources (von Bastian et al., 2022). While these distinctions are theoretically useful, there is no consensus on how to define the neural substrates of these different approaches. For example, while Lovden considers increased myelination a structural change with functional consequences (i.e., plasticity), von Bastian and colleagues interpret increases in white matter integrity following training as potentially representing improved efficiency between existing structures, and as such not a change in “capacity”.

However, few studies actively measure the brain using neuroimaging alongside cognitive training, limiting investigation into the changes underlying successful training effects. A meta-analysis of 14 studies found that cognitive training resulted in changes in brain activation in a brain network involved in the performance of demanding cognitive tasks (Duda and Sweet, 2020). A systematic review of neuroimaging measures that are linked with the effects of cognitive training identified increases and decreases in both the structure and function of a range of brain regions (with many not overlapping across studies), with two "high quality" studies highlighting changes in hippocampal functional connectivity (Ten Brinke et al., 2017), and a more recent review similarly found both increases and decreases in functional connectivity that varied by brain network, as well as increases in cortical thickness and grey matter volume (Beishon et al., 2020).

To specify more clearly the neural mechanisms involved in cognitive training improvements, we argue that large scale brain topology is an appropriate level of analysis to look for neural correlates of effective training interventions. Importantly, we are not suggesting that there are not local changes in brain activity or structure that are important for understanding cognitive training improvements. However, we believe that broad training effects in particular are reflected in network-level and whole-brain metrics that have been shown to capture large-scale neural changes that result from dementia pathology (Vanasse et al., 2021) and are reliably linked to behavior (Fox, 2018). Looking at brain topology also removes some of the ambiguity surrounding the interpretation of neural mechanisms that occurs in neuroimaging research in general, and in aging research more specifically. Both increases and decreases in brain activation are often interpreted as beneficial depending on how a specific intervention relates to neural changes and how these changes relate to behavioral improvements. These interpretations may be mechanistically meaningful (e.g., reflecting adaptive patterns of activation changes over time; Huntley et al., 2017), but it is difficult to establish whether this is the case in individual studies, and

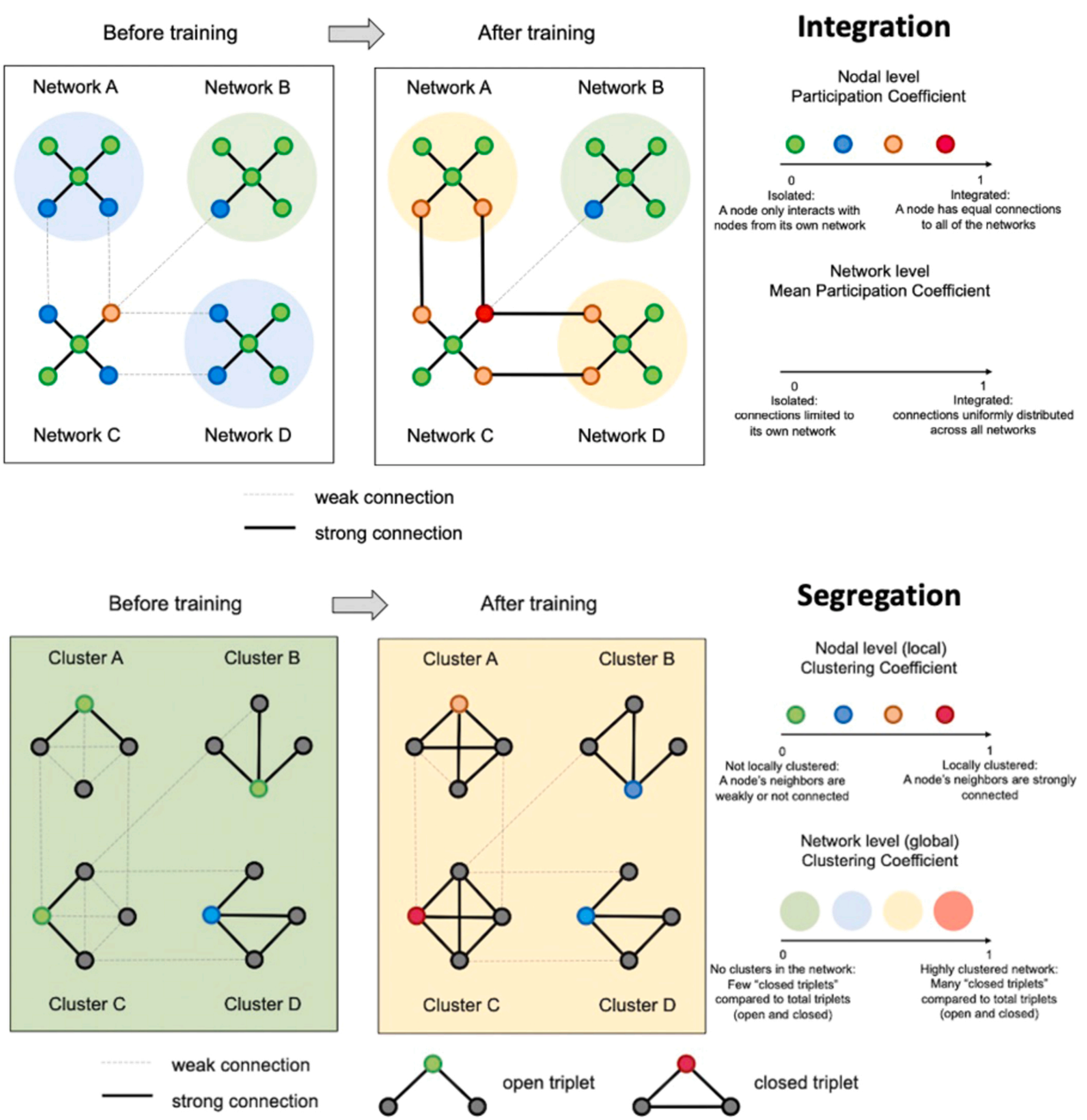

Fig. 3. Schematic overview of network-level Participation Coefficient (upper) and Clustering Coefficient (lower) change between before and after a cognitive training.

to compare across studies with opposing results. For example, the recruitment of additional regions for task performance in older adults has been interpreted both as compensatory and as maladaptive (Morcom and Johnson, 2015), and it is often unclear whether the goal of brain aging interventions are to compensate for brain aging, reverse brain aging (i.e., return the brain to a youth-like profile), or improve cognition via any neural mechanism that emerges. By focusing on a single aspect of optimal whole-brain functioning; the balance of integration and segregation, we hope to improve the comparability of findings across the cognitive training literature, as well as improve the ability of cognitive training to induce broad training effects.

The brain exists in a careful balance between integration and segregation: a topology with many short-range connections organized into functionally specialized modules (i.e., segregation) with a small number of long-range connections linking them enables it to transfer information efficiently with a minimal wiring cost (i.e., integration) (Fig. 3). Selected brain regions have been identified as part of a “diverse club”, defined by high participation coefficient at rest, meaning they connect to a range of networks and play a key role within this topology by facilitating the integration of information between functionally specialized modules. This type of integrative processing is particularly important for the types of complex cognitive functions that are most at-risk of dementia, including those that engage cognitive control processes in service of efficient memory performance. Damage to these regions is particularly detrimental to a broad range of cognitive processes, suggesting that the capacity of the brain to integrate information via these regions is highly domain general. Alzheimer’s Disease is thought to act primarily by damaging these hub regions in the brain, with an outsized effect on large-scale brain topology (Yu et al., 2021). Interestingly, a recent framework suggests that baseline modularity, a graph theory index that captures how the brain divides itself into functionally specialized modules, may be a baseline biomarker for predicting the likely success of interventions that rely on changing brain plasticity (Gallen and D’Esposito, 2019). Diverse club regions play a critical role in enabling modularity by connecting functionally specialized networks via a relatively sparse number of between-network connections, supporting integration while maintaining the overall modular organization of the brain. This topology allows the brain to move between integrated and segregated states in line with the demands of the environment, for example, by segregating modules for specialized functions such as motor performance and integrating across modules for complex tasks such as working memory. In situations where modularity is preserved, enhancing participation coefficient, specifically in networks containing diverse club regions, via cognitive training may facilitate broad training effect by improving a broad range of complex cognitive functions. Literature suggests that diverse club regions appear to show preserved connectivity at least in mild cognitive impairment (MCI). In our recent study (Chen et al., 2022), we found that enhancing the resting-state participation coefficient of the ventral attention network explained how a visual-oriented SOP training induced transfer to working memory, a non-trained domain (i.e., far transfer effect) in older adults with MCI.

Alternatively, in another paper we found that a unique subset of older “learners”, individuals that showed improvements across a range of executive functions as well as episodic memory (potentially reflecting broad training effects), appeared to improve via increases in clustering coefficient of structural connections in specific regions (i.e., right caudal anterior cingulate cortex, right supramargnal gyrus, left postcentral gyrus, left putamen, left thalamus) (Chen et al., 2021). Clustering coefficient is a measure of segregation, suggesting that for certain individuals bolstering local connections may be critical to enhancing broad cognition rather than, or potentially in addition to, improving integration. Understanding how to best restore optimal network efficiency via cognitive training will be a key goal of future research in this area. Current findings show that it is not necessarily as simple as increasing either integration or segregation of the brain. Instead, research needs to understand the specific role certain nodes and connections play in the network in healthy individuals and work to restore, or compensate for, this function in individuals at-risk for dementia. Whether individuals will most benefit via enhanced integration or segregation may depend on neurodegeneration and their baseline neural profile, and comprehensive theories of cognitive training mechanisms need to account for these individual differences.

The concept of small-worldness (Bassett and Bullmore, 2006; Kukla et al., in press), a network property related to an optimal balance between segregation and integration, might be particularly useful in comparing across individuals and determining whether increased segregation or integration is likely to be beneficial. We believe that changes in brain topology measures at rest represent changes in “plasticity” as defined by Lovden as critical for long lasting improvements in cognitive function, and are additionally captured by von Bastian and colleagues’ definition of “efficiency” via which they propose cognitive training predominantly acts (Lovden et al., 2011; von Bastian et al., 2022). However, it is yet unclear whether these changes represent more strategic, or knowledge-based, improvements, or whether they act via changes in processes, another critical distinction highlighted by both Lovden and von Bastian. Task performance similar to that required during cognitive training has been shown to drive the brain between integrated and segregated states (Fransson et al., 2018; Shine et al., 2016). Extended practice dynamically moving the brain between these two critical aspects of brain topology as occurs during cognitive training programs (Finc et al., 2020) could be essential in re-balancing the brain if the capacity to engage either state has been damaged. Importantly, episodic memory (which is a key at-risk process in many forms of dementia) has also been shown to require integrated whole-brain neural processing (Geib et al., 2017), providing a potential mechanism for the transfer of training effects to episodic memory and for broad training effects more generally (Wang et al., 2021). Understanding precisely how training causes changes in brain topology, and how these changes result in behavioral improvements is a key goal of future research. There is some evidence that cognitive tasks can be optimized to target specific brain metrics, which could include segregation, integration, or small-worldness, using real-time feedback during neuroimaging (Lorenz et al., 2017). Understanding how changes in topology are reflected in peripheral markers of brain function, e.g., heart rate variability (Chen et al., 2020b), will be critical to improving accessibility moving forward given the lack of scalability of neuroimaging techniques (Turnbull et al., 2022), and may enable improved optimization that can occur in the real world during training (see section on personalization).

5.2. Leveraging positive affective states and mindfulness might strengthen the effect of training

A shift towards positive affect is a common aging phenomenon that might also be leveraged to improve training outcomes. Older adults have been shown to attend to more positively valence stimuli (Kehoe et al., 2013), and avoid more negative stimuli (Brassen et al., 2011), than their younger counterparts. Accordingly, the ventral attention network, default mode network, and amygdala tend to activate more to positive stimuli (Brassen et al., 2011; Kehoe et al., 2013; Ren et al., 2017) and show attenuated activity to negative stimuli (Bangen et al., 2014) in old age. In younger adults, this emotion-embedded cognitive enhancement has been observed most strongly for negatively valenced stimuli—an effect that appears to be reduced or absent in older adults (Murphy and Isaacowitz, 2008). Instead, studies have found that older adults are more likely to recall and recognize positive stimuli (Leigland et al., 2004). It has been suggested that this relates to age-related differences in how cognitive control processes in the prefrontal cortex are engaged during encoding (Joubert et al., 2018). Socioemotional Selectivity Theory proposes that older adults prioritize emotional goals as they age (Carstensen, 1992), and it has been suggested that building interventions with this in mind may lead to improved adherence and performance in older adults. Specifically, using feedback that focuses on participants' strengths, personal resilience, and fulfilment of current emotional goals (e.g., allowing them to "savor the moment") rather than future benefits may appeal more to older adults (Carstensen and Hershfield, 2021). This is in line with research showing that older adults are more "mindful" than their younger counterparts (Fountain-Zaragoza et al., 2018), and spend more time thinking positive thoughts about their current task rather than mind wandering about the future (Mckeown et al., 2021; Turnbull et al., 2021). This effect is particularly pronounced in subjectively demanding tasks, suggesting it could be exploited by cognitive training paradigms. Incorporating stimuli and feedback that encourages older adults to see cognitive training as enjoyable in-the-moment, potentially via the idea of mindfulness, rather than beneficial for their future cognition, could boost training effects, potentially via ventromedial prefrontal cortex-centered networks known to be important for motivation and value judgment that have been proposed to support resilience in older adults (Feder et al., 2019). This is supported by research showing that mindfulness training improves cognitive performance (Isbel et al., 2020) and positively framing instruction for cognitive training enhances adherence to cognitive training in older adults (Harrell et al., 2021). Incorporating mindfulness-based concepts into cognitive training may suggest a potentially fruitful avenue for research. It is important to note that older adults at-risk for dementia often shown neuropsychiatric symptoms including anxiety, depression, apathy, and irritability that interfere with adherence to interventions. Directly intervening to improve the emotional states of these participants via co-occurring therapy (e.g., Cognitive Behavioral Therapy) might be necessary to leverage the benefits of positive affective states on cognitive training outcomes, another example of the importance of population-informed designs.

6. Personalizing cognitive training to the individual and their adaptation capacity

So far, we mostly considered training design at its macro level. Even for the best designed cognitive training, it will only be effective if it engages plasticity in a way that avoids training brain processes in a manner that is highly specific to training experience. Emerging cognitive intervention theories emphasize the importance of prolonged "mismatch" between a person's brain capacity and cognitive training challenges for inducing neuroplasticity (Lovden et al., 2011). An appropriate "mismatch" refers to a state where the challenges in cognitive training exceed brain capacity by a manageable amount and eventually leads to positive neuroplasticity. Currently, learning during cognitive training (indexed by accurate response across consecutive trials) is the main indicator of amount of "mismatch". When a person's brain capacity far exceeds cognitive training challenges, no effort is required for learning tasks and the brain will conserve energy without expanding. In contrast, when the brain capacity falls far short of cognitive training challenges, the task may overwhelm a person, resulting in no investment on learning. Moreover, when the length of "mismatch" is unrealistically long, effective learning will decline while fatigue increases (Nolte et al., 2008). In the aging population, learning during cognitive training can be influenced by multiple unmodifiable factors related to cognitive reserve (e.g., IQ, education) and neurodegeneration (Stern, 2012). Individuals with high cognitive reserve can demonstrate a quick improvement in task performance without neuroplasticity effectively taking place (Stern, 2012). Hence, pseudo-learning under these circumstances may interfere with the efficacy of existing cognitive trainings. It is essential to identify components that can enhance the reliability of learning to ensure it reflects genuine adaptation to "mismatch". An individual's adaptation capacity to environmental demands is critical for determining the appropriate length and amount of "mismatch" for individuals (Lovden et al., 2011).

6.1. Monitoring within-individual mismatch via adaptation capacity

Flexible adaptation to physical stressors or changing environmental demands is critical for maintaining a person's everyday function, health span, and longevity (Epel and Lithgow, 2014). In response to exteroceptive stimuli, such as cognitive training tasks, dynamic neurophysiological (i.e., interoceptive) processes involving the parasympathetic (PNS) and sympathetic (SNS) branches of the autonomic nervous system (ANS) are activated in efforts to restore homeostasis via adaptation to the stimuli. A recent meta-analysis concluded that in response to different types of exteroceptive demands (e.g., cognitive, social, emotional, physical), SNS activates and PNS withdraws to a roughly equal extent (Brindle et al., 2014). The central autonomic network (CAN), a proposed set of brain regions that are associated with ANS function, and ANS are tightly and dynamically connected via anatomical, functional, and hormonal pathways. Cumulative work suggests the integrity of CAN is critical for top-down regulation of ANS flexibility (Beissner et al., 2013; Lin et al., 2017b). Several key cortical (i.e., ACC and insula) and subcortical regions have been linked to the central regulation of ANS flexibility (Beissner et al., 2013; Lin et al., 2017b), forming several essential cortical (i.e., ventral attention network/salience network, limbic network, and default mode network) and subcortical (i.e., noradrenaline system for SNS and acetylcholine system for PNS) subnetworks within the larger CAN. These regions might switch their involvement with networks during the change of status (e.g., off- to on-task) or type of stimuli (e.g., physical vs. cognitive). For example, when a person first encounters a cognitively challenging task seen in cognitive training, significant neural synchronization would be engaged to adjust to the task. When an effective strategy has been developed, this may involve a reorganization of neural communications (Chen et al., 2020a; Lin et al., 2017a). The timeframe for these adaptations can vary across individuals. Also, how resilient or vulnerable CAN is to typical or pathological brain aging may determine the degree of ANS flexibility in at-risk populations. For example, a shift from medial PFC, including ACC, to lateral PFC in the typical aging process may lead to less ANS responsivity to emotional stimuli, or cause more effort to be required to respond accurately to cognitive stimuli (Reuter-Lorenz and Park, 2014).

Previous work in our lab has established that signals in physiological recordings that reflect ANS function provide a measure of adaptation capacity that predicts improvements following cognitive training (Chen et al., 2020a). These signals also related to changes in brain function in regions known to be involved in autonomic regulation. Additionally, we have found that related autonomic measures can be modified by cognitive training, suggesting that these markers may provide a means of improving transfer effects by identifying within-subject mismatches between capacity and task requirements (Lin et al., 2020). Specifically, an initial decrease or suppression of the PNS response occurs when the brain circuits must allocate neural resources in response to the stimuli, thereby suffering from diminished capacity to exert control over the PNS. The subsequent increase or rebound phase represents the return of neural resources in regulating the PNS when individuals have adapted to the stimuli, and are no longer challenged enough to require additional neural resources. This entire process—suppression and then rebound of the PNS (Fig. 4) —in response to a challenge reflects adaptation capacity. Under the same cognitive load from a training task, individuals with more capable brain resources may have less suppression and faster rebound and less learning. Further, when older adults can reallocate brain resources, as seen in the typical aging-associated neural dedifferentiation or posterior-to-anterior shifting, to compensationally attend exteroceptive regulation of PNS, the exteroceptive PNS pattern may remain. However, among those with dementia pathologies that affect the brain's functional compensation, PNS during the first phase would show greater decline in order to divide enough resources to attend the stimuli, and/or longer time to rebound during the second phase. Hence, monitoring the ANS pattern may help personalize an effective learning experience. Exactly how the process of suppression and rebound shown

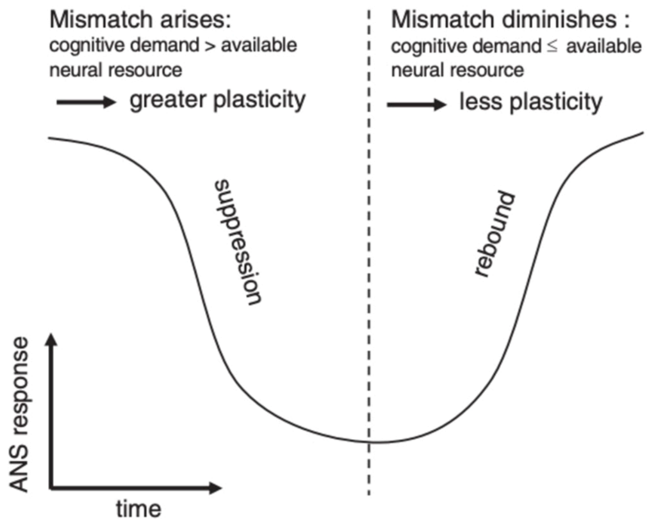

Fig. 4. Schematic overview of ANS response over a cognitive training task.

in Fig. 4 results in increased cognitive resources (and changes in brain topology) from cognitive training is currently unclear, and is it unknown to what extent the process of maintaining mismatched states during training leads to lasting changes in autonomic signals. McEwen and Gianaros (2011) propose that in the case of stress, normal physiological responses result in a return to a baseline physiological state (as seen in Fig. 4), but outline how repeated exposures can lead to changes in this response, either via habituation, a lack of rebound, or inadequate responses to novel stressors. Future work should examine how repeated exposure to a minor cognitive stressor such as demands from cognitive training leads to changes in both the autonomic response itself and brain networks known to be involved in regulating these responses, and how this might increase cognitive capacity and change brain topology over time.

Monitoring adaptation capacity may also be useful to better understand conflicting evidence surrounding the dose-response relationship in cognitive training research. There is evidence that it may not be as simple as more training leading to more improvement, as suggested by the finding that fewer training sessions per week may be more beneficial (Lampit et al., 2014). There are theoretical reasons to think it might be the case that more training is not always better: extensive mismatches can lead to fatigue (Nolte et al., 2008) that interferes with learning and plasticity. This is more likely to occur in individuals at-risk for dementia that show higher levels of fatiguability. A study by Huntley et al. (2017) showed that there was potential for plasticity in individuals with Alzheimer's Disease that was reflected in reduced brain activation following cognitive training. They suggested that this may reflect a U-shaped curve that occurs during cognitive training, with activity increasing during the early stages of training and decreasing as training increases. This pattern may relate to adaptation capacity, and it is currently unclear exactly how the short-term dynamics (i.e., suppression and rebound during a single session) and long-term dynamics (i.e., U-shaped curve seen in brain activity) overlap to reflect adaptation capacity during training. Monitoring adaptation capacity and analyzing both within-session and across-session dynamics will be critical to determining the best dosages for cognitive training, which are likely to be population- and individual-specific, and may help to devise objective measures of dosage of cognitive training. Measuring dosage in terms of minutes, hours, or sessions (as is commonly done now) may be a poor way of capturing how much meaningful cognitive training is being completed: participants could spend an hour a day engaging in cognitive training but if they are not maintaining an appropriate mismatch this may represent 0 min of effective training.

6.2. *Effective mismatch can lead to broad training effects*

It is important to keep in mind that generating a mismatch is not sufficient for generating broad training effects: the mismatch also has to occur over a broad set of processes that are likely to representative of target skills in the real world (Seitz, 2018), improvements in which would lead to broad transfer. This fact may necessitate monitoring-personalization loops that can identify (A) whether a mismatch is occurring between brain capacity and cognitive training challenges and (B) whether these mismatches are occurring over a range of neural processes that are most likely to represent the real-world processing needed for broad transfer. For example, a set of challenges may be presented to a participant and monitoring may suggest a prolonged mismatch, however, the prolonged mismatch does not necessarily lead to broad training effects. While part of this can be solved using carefully designed and population-informed paradigms that include significant variability, it will also require personalization of the challenges based on participant performance. Monitoring-personalization loops could be developed that suggest the optimal next set of challenges based on mismatch to the previous set. For example, a participant that seems to show limited mismatch on tasks that overlap in terms of their reliance on working memory may be presented with a set of challenges that sample a broad range of cognitive domains other than this "mastered" working memory process. This approach is consistent with the observation that novelty and variability are essential in predicting neuroplasticity in animal studies (Li et al., 2013). To ensure broad training effect-appropriate mismatches, it may be critical to include variability in cognitive training, both in terms of challenged processes and difficulty; for example, by including simple trials even when the overall difficulty of the task has increased and performance is good. Upcoming challenges can be informed both by performance and markers of mismatch, as well as by iterative processes directly aimed at the goal of increasing performance equally across the representative set of tasks (Seitz, 2018) identified as most likely to lead to broad training effects in the target population. Interestingly, it is an open question the extent to which mismatches identified via the monitoring of markers (e.g., ANS flexibility) will reflect "difficulty mismatches" in the traditional sense or "variability mismatches" that reflect the brain's inability to find a specific solution to the problem at hand. However, including different designs with both traditional staircases and pseudo-random (broad training effect informed) variability will help to understand which mismatches best encourage broad training effect and how this reflects neural processing. Attention will also need to be paid when deciding on specific combinations of novelty, variability, and adaptation to the feasibility of specific designs in old adults at-risk for dementia. As previously stated, individuals with dementia often need to start with pen and paper approaches, and are much less likely to tolerate novelty and variability than younger adults. Carefully designing personalization approaches that take into account both mechanisms of mismatch-based improvements in cognitive ability and participant tolerance levels/engagement will be necessary to maximize effectiveness.

7. Conclusions

In summary, we argue (see Box 2 for a summary of recommendations) that producing an effective broad training effect from cognitive training in older adults, especially those at risk for dementia, relies on developing challenge sets that are population-informed, based on an understanding of individual differences (i.e., in brain networks underpinning sensory, cognitive, affective process, as well as pathology/neurodegeneration), as well as personalization (i.e., by monitoring within-individual dynamics to adapt to the training activities). Together, through constructing and modifying these two aspects of training, essentially the search space of challenge sets and how they are selected throughout the training program, we can create appropriate

Box 2
Recommendations for future cognitive training research.

Based on the framework proposed in this review, we have several suggestions for how to improve cognitive training interventions for brain aging:

1. Develop challenge sets for cognitive training based on cognitive processes that are robust to pathology and neurodegeneration in the specific target population.
2. Rely on cognitive training paradigms that involve multi-sensory stimuli and learning.
3. Analyze whole-brain topology both at baseline and following training to establish both starting levels of segregation and integration across individuals and how these are changed by the specific cognitive training program being used.
4. Leverage positive affective states by focusing on the benefits of cognitive training for current emotional well-being in older adults using mindfulness frameworks, and focus on ensuring training is positive emotional experience via the use of affective stimuli, rewards, and support (possibly including therapy for individuals with affective symptomology).
5. Monitor and personalize cognitive training by using measures of adaptation capacity (ideally using scalable devices such as heart rate sensors) to ensure a mismatch between participant capacity and cognitive training demands.

Importantly, we believe interventions should be purposefully aimed at improving broad training effects as an overarching goal. Meaningful clinical improvement can be operationalized in several ways: improvement in cognitive and non-cognitive behaviors using clinically established assessments, newer generation digital cognitive assessments, or improvement in everyday function. Using a range of measures and attempting to capture real-world clinically relevant outcomes is critical to improving the impact of cognitive training.

mismatches that lead to changes in brain topology, which is the foundation for producing broad training effects. We propose that cognitive training programs will be more effective if they are based on mechanistic understanding and are informed by knowledge of population neurodegeneration that can interfere with plasticity in those most at risk for dementia. To cause broad training effects, these programs should target multi-sensory PS/A that is domain general and relatively preserved in the early-mid stages of dementia, and is known to activate networks with large numbers of diverse club regions that facilitate integration during complex cognitive functioning. Including emotional aspects to training that are also preserved in older adults and interact with adherence and motivation is also likely to broaden training effects, and may help to regulate stress responses to mismatch to reduce negative influences on neuroplasticity. Training should maintain an appropriate mismatch throughout the intervention period, which requires continuous monitoring of participant adaptation capacity. In this context, monitoring ANS function may be particularly convenient. Overall, it is important emphasize variability and diversity, both in the design of the interventions and their implementation.

Data Availability

No data was used for the research described in the article.

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