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NEUROBEHAVIORAL GRAND ROUNDS—INTRODUCTION

Considering how combinatorial interventions may promote neurocognitive plasticity

MICHELLE C. CARLSON

[1]Department of Mental Health, Center on Aging and Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Dementia is a looming and costly target for treatment and prevention given its current irreversibility. In the United States, the prevalence of Alzheimer's disease (AD) is expected to rise fourfold, to 8.6 million, over the next 50 years (Ziegler-Graham et al., 2008). Effective interventions are critically needed in early AD and preclinical stages of mild cognitive impairment (MCI; Petersen et al., 2001), when neural architecture may be sufficiently plastic, to help slow declines in both cognitive and independent functioning. At present, acetyl cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, and galantamine) remain among the most effective pharmacologic agents to treat clinical symptoms of AD. ChEIs increase neural plasticity through increases in intracellular calcium to improve the efficiency of synapses broadly (Gu, 2003; McCormick & Prince, 1985). However, long-term treatment with donepezil in MCI patients has not been efficacious in mitigating progression to AD (Jack et al., 2008; Petersen et al., 2005).

The introduction of behavioral cognitive training interventions in early AD and MCI is not without challenges either and has yielded equivocal support (Clare et al., 2003). Such interventions, as currently designed, train to a specific skill and have observed limited transfer and short-lived cognitive benefits (Loewenstein et al., 2004; Verhaeghen et al., 1992). In healthy older adults, the largest randomized trial of process-specific cognitive training, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study (Jobe et al., 2001), led to improved or maintained training-specific gains in memory, inductive reasoning, or speed of processing outcomes through 2- and 5-year follow-ups (Ball et al., 2002; Willis et al., 2006). The reasoning training arm also resulted in less self-reported functional decline. However, there was no transfer of training, thereby restricting yield for more generalized benefits.

Correspondence and reprint requests to: Michelle C. Carlson, Department of Mental Health, Center on Aging and Health, The Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument Street, Suite 2-700, Baltimore, Maryland 21205. E-mail: mcarlson@jhmi.edu

In addition to limited transfer, recruitment to and implementation of cognitive interventions are more labor, resource, and cost-intensive than are pharmacologic interventions. As a result, any null findings may serve to further dampen enthusiasm for future efforts. In this context, it is important to consider how to optimize cognitive training effects in order to boost memory and other abilities important to independent function. Some studies have recently found that memory strategy training and socialization (Bottino et al., 2005) and multidomain cognitive test training (Rozzini et al., 2007) produce evidence of short-term benefit in MCI and AD patients taking ChEIs.

In this issue of *JINS*, Gonzalez-Rothi et al. report on an innovative Phase I study over a 3-month interval in six patients with probable AD and taking donepezil. They theorized that this ChEI may potentiate learning during daily life and that targeted learning opportunities may amplify the effects of ChEI on language naming abilities in AD. These individuals participated in targeted word production practice using an "errorless learning" strategy (Baddeley & Wilson, 1994; Bottino et al., 2005). Briefly, following baseline assessment of confrontation naming ability, participants received two sequential types of confrontation naming training that varied level of trainer support. In the first "simultaneous" condition, the trainer named the picture as it was presented, and in the second "delayed" condition, the trainer waited 3 s to allow participants to name the object, if able. Three of the six participants (50%) showed significant improvements in verbal naming of trained items relative to baseline. No improvements were observed for a control, Clock Drawing, task. Nonresponsiveness to training among the other three participants may have been due to differences in baseline dementia severity, as indexed by poorer global and domain-specific cognitive functions, and living conditions. Overall, these findings suggest that cognitive training may be effective when paired with ChEIs. These promising initial findings in individuals with early AD provide compelling support for next-level studies using this combinatorial intervention approach, randomizing AD and MCI patients to a combined or a donepezil-only control group.

This Phase I study is important in highlighting the potential to initiate cognitive training during a critical "window," when implementation of a ChEI in AD patients increases neural plasticity (Gu, 2003; McCormick & Prince, 1985) and potential responsiveness to new learning. This period of enhanced neuroplasticity provides the ideal neural environment in which to introduce cognitive training platforms, such as the targeted errorless learning method, here. The errorless learning method is innovative in reducing one's opportunity to attend to and practice incorrect responses. Furthermore, this method may serve as an external executive assistant in inhibiting selection of distracting tangential responses by helping one direct attention and memory resources solely to target information.

In addition to training process-specific abilities, such as language, Gonzalez-Rothi et al. indicate that other cognitive enrichment programs could be equally applied in conjunction with ChEIs to optimize learning opportunities. We now know the great potential for brain plasticity into later life in animals (Briones et al., 2004; van Praag et al., 1999) and humans (Carlson et al., submitted) in direct response to environmental enrichment.

Recent studies of preclinical AD show that deficits often emerge in multiple domains, including memory (Small et al., 2001), executive function (Albert et al., 2001; Chen et al., 2000), and speed of processing (e.g., Barberger-Gateau & Fabrigoule, 1997). Executive functions and associated prefrontal cortical regions appear to decline disproportionately faster than other abilities with age (Goldman-Rakic & Friedman, 1991; Raz, 2000). Joint comparisons of cognitive declines with age further suggest that executive functions may decline more rapidly than memory (Carlson et al., 2009). In cross section, executive functions are selectively associated with independent activity of daily living (IADL) functional difficulty (Carlson et al., 1999; Grigsby et al., 1998; Johnson et al., 2007). Executive functions have also predicted incident and worsening functional difficulty over 6 years (Johnson et al., 2007). These findings suggest that executive functions may contribute to memory and functional declines and may be amenable to interventions that promote neural plasticity and learning. However, executive functions are among the least studied abilities in preclinical AD, and there are few cognitive training platforms designed to explicitly target executive planning and organizational functions important to independent function (Levine et al., 2007; Stuss et al., 2007).

These findings collectively highlight three potentially important features for the next stage of cognitive interventions, whose efficacy may be amplified in MCI and AD when paired with ChEIs. First, environmental enrichment in daily life, in combination with ChEI, may train directly to abilities important to maintaining functional independence. Ironically, the diagnosis of AD, and corresponding introduction of donepezil, may coincide with a resulting loss of opportunities for daily learning and enrichment through routine contact with friends, neighbors, co-workers, and adult offspring, who may live remotely. Therefore, the introduction of cognitive rehabilitation strategies and opportunities for learning and enrichment in one's community become all the more important. Second, cognitive interventions have largely focused on rehabilitation of memory and language impairments seminal to AD pathology and have yet to be designed to target those potentially compensatory executive abilities and cortical regions that appear to be most susceptible to the normal and pathologic effects of aging. Third, we have yet to understand the durability or longer term benefits of combinatorial cognitive–pharmacologic interventions post-exposure and whether they should optimally be maintained, much as prescribed medications are used to manage other chronic diseases, such as diabetes and cardiovascular disease. If cognitive enrichment is to be maintained, then programs should strive to give the brain what it consistently seeks—novelty and stimulation. Studies of one such model, entitled "Experience Corps," represent a community-based volunteer service program that trains and places teams of at-risk older adults in Baltimore City elementary schools to help children with reading achievement, library support, and classroom behavior (Fried et al., 2004). In a pilot trial and pilot functional neuroimaging study, 6 months of exposure to this program led to improvements in executive function and memory (Carlson et al., 2008) and associated changes in prefrontal cortical regions (Carlson et al., submitted) among those with baseline cognitive impairments. These findings offer additional support for the neuroplasticity of older individuals at elevated risk for dementia when placed in cognitively enriching settings and may represent one means by which to help ameliorate the lifelong accumulation of dementia risk factors thought to diminish cognitive reserve (Stern et al., 1999, 2003). These initial findings further highlight the potential of combinatorial interventions pairing opportunities for novelty and daily learning with effective pharmacologic agents that may amplify their effects on neural plasticity.

Identification of efficacious and effective cognitive interventions with the potential for immediate benefits and large-scale dissemination and adherence are increasingly critical as we face a demographic upswing in the aging population and a corresponding surge in the number of individuals living long enough to develop AD. Given the current and projected health care costs associated with managing this slow progressive disease, effective strategies that can even modestly shift the onset and course by 6 months to 1 year have tremendous potential to reduce burden at the level of the individual, the family, and society (Brookmeyer et al., 1998).

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