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SYMPOSIUM—INTRODUCTION

Introduction: A Life Course Perspective on Activity and Neurocognitive Health

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INTRODUCTION

This symposium presents work aimed at enhancing our understanding of the effects of activity—physical, cognitive, and social—on cognitive and brain health under normative (child development & aging) and neurodegenerative [multiple sclerosis (MS) and Alzheimer's disease (AD)] conditions across the life course. Some recurring themes arise across these studies. First, using sensitive neuroimaging, electrophysiologic, and histopathologic techniques, researchers are evaluating the mechanisms by which physical, cognitive, and social activities affect neurocognitive health in targeted brain regions. These findings suggest that the hippocampus, which is critical to memory formation, and the prefrontal cortex (PFC), which is fundamental to executive function and higher order thinking, are responsive to physical and other forms of activity in day-to-day life. Second, physical, cognitive, and social activities represent overlapping dimensions; understanding their benefits will require a broader conceptualization of the metrics and tools used to define activity so as to better capture the complexity of environmental enrichment shown to elicit neurogenesis and synaptogenesis in models of young and aging animals. Doing so will advance the field of cognitive intervention research and offer new perspectives into how to incorporate activity into daily life. Third, findings reported here suggest that those who are most vulnerable, whether by virtue of neuropathology, aging, or both, may derive the greatest benefits. In other words, those with the most to lose may have the most to gain from environmentally enriching physical, cognitive, and social activity.

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I introduce the life course perspective for this symposium by briefly summarizing the emerging literature linking activity to neural networks thought to be particularly important to memory and executive function from youth through late-life and disease. I then frame activity-cognition associations presented in this symposium from early and mid life (MS) to late life development when age-associated neuropathologies emerge. In addition to the known benefits of environmental enrichment on brain health in animal models (Kempermann et al., 2010; van Praag, Shubert, Zhao, & Gage, 2005), this symposium is further motivated by recent observational and intervention studies of activity among older adults with dementia and middle-aged and older adults at elevated sociodemographic risk for cognitive impairment. I conclude by proposing that this life course perspective will aid identification of common pathways by which to measure and impact neurocognitive health and thus offer novel perspectives into early intervention among the most vulnerable.

ACTIVITY AND THE BRAIN

Rapidly emerging evidence indicates that physical activity directly influences the functional and structural properties of the hippocampus, a brain region critical to learning and memory throughout the life course (Shen, Specht, De Saint Ghislain, & Li, 1994) and implicated in risk for dementia (Killiany et al., 2002). Change in hippocampal volume has been correlated with decline in memory performance and with increased risk for dementia (Desikan et al., 2009; Kerchner et al., 2010; Killiany et al., 2002; Kramer et al., 2007; Petersen, 2000). Cross-sectional and longitudinal studies have reported an inverse association between self-reported physical activity and age-related decreases in mediotemporal volume (Bugg & Head, 2011) and with mitigated rates of decline in hippocampal volume nine years later (Erickson, Raji, et al., 2010). Greater cardiorespiratory fitness has been associated cross-sectionally with greater hippocampal volume in both children (Chaddock et al., 2009) and healthy older adults (Erickson et al., 2009). In a randomized, controlled trial of exercise in healthy older adults, a walking intervention over one year increased hippocampal volume by 2% relative to 1% decreased volume in a stretching and toning control group (Erickson, Voss, et al., 2010).

The hippocampus is influenced by the PFC, the evolutionarily newest region of the brain central to integration of the past and present in anticipation of future rewards and threats, and further represents an area important for many prosocial behaviors (Diamond, 2002). PFC maturation is not complete until one's early 20s (Gogtay et al., 2004), presumably because the ability to integrate multiple streams of information requires the maturation of sensory-specific networks (Casey, Getz, & Galvan, 2008; Garon, Bryson, & Smith, 2008; Rubia, Smith, Taylor, & Brammer, 2007). This slow maturation is reflected in adolescents' tendency toward risk-taking behaviors and less consideration of the consequences of their actions (Casey et al., 2008; Steinberg, 2007). With age and experience, these priorities typically reverse and thoughts of consequences more often prevail over the moment. In later life, however, the late-developing prefrontal circuits appear to be more vulnerable than other brain regions, including the hippocampus. Studies of the aging human brain show that loss of brain volume is greater in the PFC than in posterior areas of the cortex (Buckner, 2004; Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002; Madden, 2000; Raz, 2000; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Consistent with these findings, in longitudinal study, we have found that declines in executive function preceded those in verbal memory in older community-dwelling adults (Carlson, Xue, Zhou, & Fried, 2009). In this issue, Chaddock, Pontifex, Hillman, and Kramer summarize cross-sectional evidence in children demonstrating a relationship between physical fitness, physical activity, and academic achievement, and conclude that these associations may be due to enhanced cognitive control mediated by PFC networks during this critical developmental window. Effects of physical activity, however, are not limited to the prefrontal cortex. Chaddock and colleagues also discuss associations between aerobic fitness, episodic memory, and volume of the hippocampus. Moreover, they provide evidence that physical fitness predicts performance on a memory task one year later, suggesting that the benefits of fitness extend over time. These data call for more definitive randomized controlled trials of physical activity in childhood to determine its impact on different aspects of neurocognitive development.

This symposium also provides evidence for the benefits of physical fitness and activity in response to neuronal injury in mid-life. Prakash, Patterson and Janssen have studied the relationship between physical fitness and cognitive and brain health in multiple sclerosis (MS) (Prakash et al., 2007; Prakash, Snook, Motl, & Kramer, 2010). In this issue, they report that higher levels of physical activity in patients with MS are associated with increased resting-state connectivity between the hippocampus and posteromedial cortex, two regions that are critical to memory. Higher connectivity, in turn, was associated with better memory performance, although physical activity itself was not associated with better memory in this small sample. These findings are intriguing, but their cross-sectional nature prevents causal inferences, in part, because higher physical activity may reflect less severe MS, which may likely be associated with increased resting state connectivity. Therefore, there is a clear need for intervention studies in MS that promote physical activity in daily life and evaluate the mechanisms of benefit.

MEASURING ACTIVITY IN DAILY LIFE

There is now ample evidence that enriching environments physically, cognitively, and socially promotes the emergence of new neurons and synapses in old, as well as young, animals and reduces neuronal death, especially in the hippocampus (Holmes, Galea, Mistlberger, & Kempermann, 2004; Kempermann, Chesler, Lu, Williams, & Gage, 2006). However, measures of cognitive and physical activity have traditionally focused on the frequency of an activity, under the logical premise that more of a good thing is better than less of a good thing. In our recent work, we have directly compared the utility of frequency of cognitive activities relative to the number of different stimulating activities endorsed, under the premise that number, or variety, of distinct activities may serve as an index of an active and engaged lifestyle (Carlson et al., 2011). Greater variety of participation in activities, regardless of cognitive challenge, was associated with an 8 to 11% reduction in the risk of impairment in verbal memory and global cognitive outcomes over nearly 10 years among initially high-functioning older women. Participation in a variety of lifestyle activities was a better predictor of cognitive outcomes than frequency or level of cognitive challenge. We interpreted these findings as reflecting the influence of a greater variety of environments and greater requirements to flexibly coordinating time and resources across multiple activities, in keeping with the environmental complexity hypothesis (Hultsch, Hertzog, Small, & Dixon, 1999).

A review of the epidemiologic literature on activity and risk for cognitive impairment suggests that activity in various forms promotes cognitive reserve. For example, in a 3-year follow-up study, those who participated in three or more social or leisure activities had an 80% lower dementia risk compared to those who did not participate in such activities (Fabrigoule et al., 1995; Helmer et al., 1999). The study also reported a stepwise reduction in dementia risk with increasing number of activities endorsed. In the Cardiovascular Health Study, energy expenditure in kilocalories did not predict reduced dementia risk after adjustment for demographic factors, whereas variety or number of functional and exercise activities, adjusted for covariates and energy expenditure, was a significant predictor among those without genetic risk for AD (i.e., Apoe-e4 allele carriers; Podewils et al., 2005). These data suggest that variety may serve as an index of an active and engaged lifestyle, and may provide neurocognitive benefits by exercising PFC-mediated executive functions and hippocampally mediated memory functions, as postulated above.

In keeping with the known benefits of social networks (Fratiglioni, Paillard-Borg, & Winblad, 2004), a growing body of evidence also suggests that greater mid- and late-life social engagement is associated with better cognitive and physical health and greater longevity (Carlson, Helms, et al., 2008; Saczynski et al., 2006). In this issue, James, Wilson, Barnes, and Bennett report that, among a large, community-based cohort of older adults initially free of dementia, more frequent social activity was associated with reduced rates of cognitive decline across several domains over 5 years, independent of physical and cognitive activity. Because their analyses adjusted for size of social network, their findings speak to the unique value of social activity. Benefits are postulated to derive, in part, from navigating complex and interpersonal exchanges and the associated intellectual engagement (Hultsch et al., 1999), and through the adoption of social roles that may provide a sense of purpose in later life (Berkman, Glass, Brissette, & Seeman, 2000; Hultsch et al., 1999). Both of these areas represent emerging topics of study incorporated in the design and evaluation of a new generation of social health promotion interventions that target cognition.

ENRICHING ENVIRONMENT THROUGH MULTIPLE ACTIVITY PATHWAYS

This approach is exemplified by Experience Corps, a community-based model in which retired adults are trained and placed in teams in elementary schools with the goal of improving the academic achievement and behavioral outcomes of children during a critical period of development in reading skills (Fried et al., 2004). Through this form of volunteer activity, physical, cognitive, and social activities have been preliminarily shown to increase (Fried et al., 2004), through walking to the school (Tan, Xue, Li, Carlson, & Fried, 2006), supporting literacy and math skill, aiding behavior management and positive conflict resolution, and the need to flexibly shift between these roles (see Rebok, Carlson, Barron, Frick, & McGill, 2011). In harnessing older adults' knowledge and wisdom accumulated over a lifetime, they become simultaneously the agents of social health promotion for themselves and for the children.

A 7-month, randomized, controlled pilot trial of Experience Corps enhanced executive functions and memory among those community-dwelling older adults with poor executive function at baseline relative to matched controls (Carlson, Saczynski, et al., 2008). A pilot brain-imaging study over 6 months in Experience Corps volunteers showed improved executive function and increased task-related brain activity in the PFC relative to matched controls (Carlson, Erickson, et al., 2009). Both studies show that individuals at greatest risk for cognitive impairment maintain great potential for activity-induced plasticity. These preliminary program results are encouraging in both volunteers and among the children they serve (Rebok et al., 2004) and await confirmation in a large-scale randomized trial of the Experience Corps Program in Baltimore.

AGING AND NEUROPATHOLOGY: ALZHEIMER'S DISEASE

Although the causes of AD are not well understood, observational studies consistently demonstrate that risk may be modified by education, physical activity, and cognitive activity (Barnes & Yaffe, 2011; see Qiu, De Ronchi, & Fratiglioni, 2007, for a review). Verghese and colleagues have previously shown in the Bronx Aging Study that, among older adults who ultimately developed dementia, participation in cognitively stimulating leisure activities delayed the onset of accelerated memory decline. In this issue, Pillai, Hall, Dickson, Buschke, Lipton, and Verghese show that participation in crossword puzzles delayed onset of accelerated memory decline by 2.5 years compared to non-puzzlers. However, once memory decline began, the rate of decline was more rapid for crossword puzzlers than for non-puzzlers. These findings are consistent with the cognitive reserve hypothesis, which postulates that cognitively stimulating activities may help delay the onset of clinical deficits until the point that pathological burden overwhelms reserve (Stern, 2009). Along the same line, we have observed in the population-based Cache County Dementia Progression Study that weekly participation in cognitively stimulating activities early in the course of AD was associated with slower cognitive decline (Treiber et al., 2011).

An important cautionary note is the potential for reverse causality, namely, the possibility that higher levels of engagement in stimulating activities may be a reflection of less severe illness. Therefore, randomized and matched case-control intervention studies represent an important next step to elucidate whether the very pathways by which inactivity may adversely affect childhood and older adult development are the same malleable pathways by which to enrich and boost cognitive health to help circumvent advancing neuropathology.

CONCLUSIONS

Data presented here suggest that physical, cognitive and social lifestyle activity across the life course impacts cognitive and brain health in multiple ways. Exploring similarities and possible differences in findings across the spectrum of age and diseases makes it possible to further refine our understanding of the underlying mechanisms of action. Structural and functional neuroimaging methods, including the study of white matter integrity through diffusion tensor imaging (Mori, Oishi, & Faria, 2009) and functional connectivity as applied in this issue by Prakash and colleagues, will continue to be important in elucidating the relationships between activity and cognitive health.

There are many gaps in knowledge regarding the optimal doses, durations, and frequencies of physical, cognitive, and social activities that are needed to derive and sustain cognitive benefits. An important goal of future research will be to develop metrics and real-time tools to capture the doses and frequencies of activities in daily life that promote environmental enrichment and complexity and that are sustainable. Commercially available, real-time data methods, such as accelerometers and actigraphs, represent important adjuncts in this endeavor, as they are unobtrusive, place minimal burden on recall, and capture lifestyle activity with temporal and spatial precision.

There is a clear need for randomized controlled intervention trials of activity in children as well as normal older adults and those with dementia. Much remains to be learned about the specific physical or cognitive activities that contribute to cognitive health or offer resilience to pathology, and the limits of their effectiveness. At the same time, given the beneficial effects of social engagement on cognitive function in aging, there is movement toward the design of broadly applicable and cost-effective activity interventions that integrate physical, cognitive, and social components into daily life. An important objective for these studies will be to explore the interactive, and potentially synergistic, effects of different forms of activity.

We are entering a phase in which pharmacologic intervention is no longer considered the only (or even primary) line of defense in delaying and remediating cognitive decline and impairment. Capitalizing on the brain's inherent plasticity, it now appears possible to boost cognitive and brain reserves by enriching the environment through multiple types of activity in daily life. In so doing, it is possible to exploit multiple pathways by which to impact cognitive health. At the level of public health, better understanding the intersection of activity and neuroprotective health will inform the effective design of infrastructures and programs that integrate and sustain activity in daily life in doses sufficient to promote optimal executive and memory function across the life course.

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