
SHORT REVIEW

Truly Cross-fit: The Association of Exercise and Clinical Outcomes: Introduction to a JINS Special Section

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Abstract

We introduce a JINS special section inspired by a symposium presented at INS 2020 in Denver. The symposium was entitled *Truly Cross-fit: The Association of Exercise and Cognitive Reserve*. The collection of papers herein spans diverse methods, a range of developmental and clinical conditions, and a variety of outcomes all reflecting on the association of exercise and cognition-related outcomes. Taken together, the studies in this Special Section direct us to the variety of dimensions to be considered in understanding this association including what mode, intensity, duration, and timing of physical activity and aspects of age, sex, genetics, baseline characteristics, and disease status moderate these findings. We hope this Special Section will not only provide a framing for important future research on exercise and clinical outcomes but also inspiration to pursue them.

Keywords: Physical exercise, cognition, function, methodology

A 2015 JINS Special Issue focused on physical activity and brain plasticity. In that Issue, organizers (Smith, et al., 2015) undertook a panoramic exploration of the impact that physical activity and exercise have on the brain's plasticity, broadly construed. The articles contained in the 2015 Issue spanned a variety of paradigms, modalities, and outcomes. From single bouts of intensive exercise to lifelong leisure physical activity; from resistance training to exergaming; and from cognitive measures to top shelf brain imaging. In sum, the works presented in that Issue expanded our understanding of the myriad ways that physical activity and exercise contribute to improved (or preserved) brain health in humans, even in the context of underlying disease.

An invited symposium at the INS annual meeting in Denver in 2020, entitled *Truly Cross-fit: The Association of Exercise and Cognitive Reserve*, serves as the basis for this special section of JINS. The symposium was initiated by Dr. Okonkwo and organized and chaired by Dr. Smith. Presentations in that symposium included those of Drs. Jill Barnes, Kaitlin Cassaletto, Vonetta Dotson, and Aliyah Snyder,

as well as commentary and data shared by Dr. Smith. The collection of papers herein spans diverse methods of acquiring knowledge (literature review, randomized single-intervention pilot clinical trial, multicomponent comparative effectiveness study). It considers a range of developmental and clinical conditions including mild brain injury, cognitive aging, late-life depression, pre-clinical Alzheimer's disease, and mild cognitive impairment (MCI) of nonspecific etiology. The studies provide a range of methods for establishing the association of an independent variable linked to physical activity with dependent variables related to symptomatology, cognitive function (including global cognition and domain-specific cognitive abilities), and daily function. The studies are summarized in Table 1. These study variations provide the opportunity for a convergence of findings that strengthen our understanding of the phenomena of interest. However, the study variations also result in divergent observations. These divergent observations may result from methodological differences, or could reflect on variations in the association of physical exercise and cognition. However, even the latter case allows us to modify, broaden, and improve our conceptual models.

In the first paper in this series, Dr. Jill Barnes and her research group (Barnes et al., 2021) provide a review of

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Table 1 Summarizes the studies included in this special section according to design, population, exposure type, outcome, and findings

Study	Design	Target population	Exercise-related exposure	Outcome	Findings
Barnes et al.	Review	Cognitive aging	Various	Arterial stiffness (and vasoreactivity)	Promising findings in older adults for habitual exercise benefiting cerebrovascular makers associated with brain health
Dotson et al.	Review	Late life depression	Various	Cognition	Promising findings for the effect of progressive exercise on cognition, and evidence that combined cognitive and physical exercise is better than either alone
Snyder et al.	Pilot clinical trial	Mild traumatic brain injury	7-days of stationary cycling	Concussion symptom, memory and processing speed	No group differences
Shandera-Ochsner et al.	Cluster randomized comparative effectiveness	MCI	10-days of yoga as part of multicomponent trial	Daily function	Significant benefit from yoga

the putative but foundational physiologic mechanisms by which exercise could impact brain and cognitive function. They note two prevailing and complementary theories, the neurogenesis hypothesis and the vascular hypothesis. They then comprehensively review research emanating from the vascular hypothesis. From their own work, the Barnes group demonstrates that cerebral arterial stiffness and vasoreactivity change in normal aging. They then review others' research which often, but not always, suggests that habitual exercise may impact arterial stiffness and vasoreactivity measures. They argue that one reason for inconsistent findings is that exercise benefits on arterial stiffness and vasoreactivity may be limited to older adults, i.e. that exercise effects in younger adults may be minimal because arterial elasticity is at peak. The Barnes group summarizes: "Arterial stiffening in the large central arteries is associated with indicators of brain health and improved by regular exercise. Therefore, the reported beneficial effects of exercise on arterial stiffness may also indicate favorable changes in the brain. Measuring cerebral vascular function offers a promising way to assess vascular health in the cerebral circulation and could be used as an early biomarker [of future cognitive decline]."

In the next paper, Dotson et al. (2021) discuss research findings suggesting that exercise may benefit cognition in late-life depression. This review provides strong evidence for the association of depression with cognitive impairment in later life and describes the neurobiological basis for this association. Dotson et al. subsequently describe meta-analysis that reveals that, when age is unrestricted, the impact of exercise on cognitive function among adults with depression was minimal. In contrast, the association of exercise with improved cognition in older adults with depression was consistently robust. They discuss how ceiling effects may limit associations in younger groups or across depression severities. Ultimately, the Dotson paper conveys the "structural and functional brain changes that are linked to both cognitive impairment and mood disruption, and explains how exercise targets these same brain changes and can thus provide an alternative or adjunctive treatment for cognitive impairment in late-life depression."

In her presentation at INS, Dr. Cassaletto reported on sex-specific effects of exercise on cognitive aging. The findings included in that presentation indicated that in a cohort of cognitively normal older adults, greater levels of self-reported physical activity were associated with lower levels of inflammatory markers and blood pressure, greater parahippocampal volume, and better performance on processing speed and visual memory measures among men but not among women. Those findings are published elsewhere (Casaletto et al., 2020).

A team led by Dr. Snyder (Snyder, et al., 2021) share results of a pilot clinical trial in a group of young adults presenting with concussion/mild traumatic brain injury. Participants were between 18 and 40 years old. In the period between 14 and 25 days post injury, they were randomized to 7 days of supervised aerobic exercise or stretching. The aerobic exercise involved 40 min of stationary bike riding on 6 of the 7 days, with a target of 70% maximum heart rate during

exercise. Groups were compared on self-reported concussion symptoms, mood, sleep, and cognitive measures involving memory and fluency. No between group differences were found, as both groups showed comparable improvement over time. These results did not support the value of aerobic over nonaerobic activity in the post-acute epoch but did suggest that the dogma of sustained rest after mTBI may not be supported by the evidence.

Shandera-Ochsner, et al. (2021) examined yoga as one piece of a multicomponent intervention program for persons with MCI and their partners. This study involves a unique comparative effectiveness design, with cluster randomization (Smith et al., 2017). This project previously reported a positive impact of yoga on informant-reported memory-based activities of daily living (Chandler et al., 2019). In the present report (Shandera-Ochsner et al., 2021), the primary outcomes were broader measures of daily function. They observed that the inclusion of yoga instead of wellness training in a multiple component intervention which included support groups, memory support training (Greenaway, et al., 2008) and computerized cognitive training (Smith et al., 2009) led to the best functional outcomes at 18-months post program.

Taken together, the studies in this Special Section direct us to the what, when, and whom of the association between physical activity and cognition. In other words, there is a variety of dimensions to be considered in understanding this association:

What are the parameters of physical activity; what is the mode of activity, the frequency, the time course, the duration, the intensity?

For whom do these associations hold? What aspects of age, sex, genetics, baseline characteristics, and disease status moderate these findings?

Is there an optimal time point in the lifespan (or in the aging process itself) when engagement in physical activity has the greatest potency for brain health? Relatedly, is it ever too late to adopt a physically active lifestyle?

If we are examining change, what is the natural trajectory of the outcome of interest and how does this impact our assessment of exercise benefit?

An important consideration for this field as a whole has to do with adherence and power. Specifically, what role does adherence/nonadherence play in the findings? Are studies sufficiently powered (not just in the usual sense of sample size but also with respect to the “dose” of exercise) to detect the effects of interest?

FUTURE RESEARCH DIRECTIONS

The INS symposium and this collection of papers ensuing from it perhaps reflects the need to develop a “precision public health” approach to understanding and implementing exercise programs for the purposes of improved cognitive and brain health. Populations with different cognitive risk profiles by virtue of age, sex, genetics, and etiology

may have greater or lesser ability to benefit from prescribed or free-living physical activity. More research is needed, and hopefully this Special Section will not only provide a framing for important future questions but also inspiration to pursue them.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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