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Omega-3 fatty acids moderate effects of physical activity on cognitive function

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ABSTRACT

Greater amounts of physical activity (PA) and omega-3 fatty acids have both been independently associated with better cognitive performance. Because of the overlapping biological effects of omega-3 fatty acids and PA, fatty acid intake may modify the effects of PA on neurocognitive function. The present study tested this hypothesis by examining whether the ratio of serum omega-6 to omega-3 fatty acid levels would moderate the association between PA and executive and memory functions in 344 participants (Mean age=44.42 years, SD=6.72). The Paffenbarger Physical Activity Questionnaire (PPAQ), serum fatty acid levels, and performance on a standard neuropsychological battery were acquired on all subjects. A principal component analysis reduced the number of cognitive outcomes to three factors: n-back working memory, Trail Making test, and Logical Memory. We found a significant interaction between PA and the ratio of omega-6 to omega-3 fatty acid serum levels on Trail Making performance and n-back performance, such that higher amounts of omega-3 levels offset the deleterious effects of lower amounts of PA. These effects remained significant in a subsample (n=299) controlling for overall dietary fat consumption. There were no significant additive or multiplicative benefits of higher amounts of both omega-3 and PA on cognitive performance. Our results demonstrate that a diet high in omega-3 fatty acids might mitigate the effect of lower levels of PA on cognitive performance. This study illuminates the importance of understanding dietary and PA factors in tandem when exploring their effects on neurocognitive health.

1. Introduction

Several modifiable behaviors influence cognitive performance throughout the lifespan. For example, physical activity (PA) is a modifiable behavior that influences brain and cognitive health. In children and adolescents, greater engagement in PA is associated with elevated cognitive performance and higher academic achievement scores (Castelli et al., 2007; Hillman et al., 2009). During mid-life, PA is associated with improved cognitive performance on tasks of memory, processing speed, and executive function (Etnier et al., 2006; Singh-Manoux et al., 2005). Furthermore, prospective and retrospective epidemiological studies suggest that PA during mid-life is predictive of cognitive outcomes in old age, and that increasing PA earlier in life may prevent or delay future cognitive impairment (Middleton et al., 2010; Rovio et al., 2005). Yet, beginning a physically active lifestyle in late adulthood is not futile; even modest amounts of PA in late life is sufficient for improving cognitive performance (Colcombe & Kramer, 2003). Improvements in cognitive function translate to PA-induced changes in brain morphology and function. For example, randomized controlled trials of PA suggest that it increases hippocampal (Erickson et al., 2011) and prefrontal cortex (Colcombe et al., 2006) volume, as well as functional connectivity of hippocampal and prefrontal regions (Voss et al., 2010), and increases task-evoked brain activity (Colcombe et al., 2004; Prakash et al., 2011). Cross-sectional studies of PA and physical fitness find similar patterns, suggesting a consistent effect on cognitive health in multiple populations and with multiple experimental designs.

In addition to the favorable effects of PA on cognitive function, other modifiable lifestyle factors may also contribute to cognitive function throughout the lifespan. For example, greater intake of long-chain, omega-3 polyunsaturated fatty acids (PUFA) was associated with better working memory, processing speed and

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cognitive flexibility in a sample of middle-aged adults (Kalmijn et al., 2004). In particular, higher exposure to docosahexaenoic acid (DHA), an omega-3 PUFA that is highly concentrated in the brain, has been associated with better performance on measures of executive function (Dullemeijer et al., 2007; Kalmijn et al., 2004). In line with this evidence, neuroimaging studies have reported that greater levels of omega-3 PUFAs are related to fewer white matter hyperintensities and greater corticolimbic gray matter volume (Conklin et al., 2007; Tan et al., 2012). Nonetheless, the effects of the omega-3 PUFA DHA on neurocognitive function appear to be less conclusive than the effects of PA.

In fact, several studies report little benefit of omega-3 intake on cognitive function (de Lorgeril et al., 1994; Pistell et al., 2010; Oksman et al., 2006), and initial randomized trials directly testing the effects of raised omega-3 intake have yielded only limited evidence of improved cognitive performance (Antypa et al., 2009; Chiu et al., 2008; Dangour et al., 2010; Fontani et al., 2005; Freund-Levi et al., 2006; Giltay et al., 2012; Rogers et al., 2008; Stonehouse et al., 2013; van de Rest et al., 2008). Some studies (Antypa et al., 2009; Bourre, 2004; Fontani et al., 2005; Gomez-Pinilla, 2008) suggest that associations between omega-3 and cognitive performance may be domain specific with some cognitive functions (i.e., executive functions) being more sensitive to omega-3 than others. However, other studies have been more equivocal with respect to the cognitive domains affected in younger and mid-life adults. For example, a six-month DHA supplementation in healthy adults aged 18–45 years found improvements in response time for working memory tasks in men, but episodic memory tasks in women (Stonehouse et al., 2013). Furthermore, a 12-week DHA supplementation with healthy adults aged 18–35 years reported no significant improvements on any of the 15 neuropsychological tests administered (Jackson et al., 2012). It is possible that some of this heterogeneity may be explained by interactions between PUFAs and other lifestyle variables, such as PA.

On the molecular level, omega-3 and PA share some similar effects. For example, in rodents DHA supplementation rescues the effect of a DHA deficient diet on D2 receptors in the striatum (Davis et al., 2010) and loss of dopaminergic cells in the substantia nigra in models of Parkinson's Disease (Bousquet et al., 2008). Likewise, rodent models demonstrate that PA affects dopaminergic function in reward pathways (Pothakos, Kurz, & Lau, 2009; Ridgel, Vitek, & Alberts, 2009; Speelman et al., 2011) and rescues dopamine depletion in hemi-parkinsonian models (Petzinger et al., 2007; Pothakos et al., 2009). Human studies of Parkinson's disease also show increased dopamine production and release (Ouchi et al., 2001) and cognitive and motor improvements with increased PA (Ridgel et al., 2009). In addition to dopamine, both DHA supplementation and PA influence the expression of brain-derived neurotrophic factor (BDNF), which promotes synaptic plasticity, cell proliferation and cell survival in humans (Erickson et al., 2011) and rodents (Wu, Ying, & Gomez-Pinilla, 2008). Furthermore, both DHA (Kadoglou et al., 2011; Nichol et al., 2008; Parachikova, Nichol, & Cotman, 2008; Yuede et al., 2009) and PA (Fotuhi, Mohassel, & Yaffe, 2009; Oksman et al., 2006) have been associated with reduced β-amyloid (Aβ) plaque deposits, a putative cause of cognitive impairment and Alzheimer's Disease (AD). Finally, both PA and DHA may regulate the expression of inflammatory cytokines (Kiecolt-Glaser et al., 2012; Rana et al., 2011; Rangel-Huerta et al., 2012); higher levels of which have been closely linked to a reduction in gray matter volume (Kopf, Bachmann, & Marsland, 2010; Marsland et al., 2008) and impaired executive function (Wersching et al., 2010) and memory (Bettcher et al., 2012) in humans.

Relative to the role of PUFAs in the inflammatory response, there is debate over the most appropriate method of quantifying arachidonic acid (AA; pro-inflammatory) and DHA (anti-inflammatory) levels in humans (Klingler & Koletzko, 2012). Since these n-6 and n-3 PUFAs are precursors of relatively pro- and anti-inflammatory eicosanoids, respectively (Wallis, Watts, & Browse, 2002), the n-6: n-3 ratio has been recommended as an index of DHA effectiveness. High ratios, reflecting a high proportion of AA to DHA, are associated with diminished physical health outcomes and increased incidence of inflammatory diseases (Hu, Manson, & Willett, 2001). Conversely, a low ratio has been associated with better cardiovascular and cognitive health (Dullemeijer et al., 2007; de Lorgeril et al., 1994).

Because of the shared neurobiological and physiological effects of PA and DHA intake, several human and animal studies have speculated about the additive or multiplicative benefits that might arise from combining omega-3 supplementation with PA (Gómez-Pinilla & Feng, 2012). For example, PA may provide an avenue by which the effects of DHA on cellular integrity and cognitive function are enhanced (Gómez-Pinilla & Feng, 2012; Wu et al., 2008). In rodents, the combination of PA and DHA supplementation (1.25% increase of DHA in standard rat chow) have additive effects on synaptic plasticity and membrane structure biomarkers in the dentate gyrus of the hippocampus, such that mice receiving both DHA supplementation and PA have greater levels of synaptic proteins than their counterparts not receiving PA (Chytrova, Ying, & Gomez-Pinilla, 2010). However, these effects were not mirrored behaviorally. Instead, physical inactivity without DHA supplementation resulted in impaired learning compared to mice with DHA supplementation, PA, or both (Chytrova et al., 2010). Studies in humans have not yet examined whether DHA levels moderate the effect of PA on cognitive performance in a similar way to that demonstrated in rodents.

The present study examined whether DHA omega-3 fatty acid levels moderate the effect of PA on executive function and working memory in humans. This report is an extension of our prior report on omega-3 fatty acids and cognitive performance (Muldoon et al., 2010), now containing an expanded sample with a focus on DHA through the AA:DHA ratio, as well as additional cognitive outcome variables and dietary covariates. We expected effects to be specific to executive function and working memory domains because these areas have been shown to be sensitive to both PA (Smith et al., 2010) and omega-3 exposure (Kalmijn et al., 2004; Muldoon et al., 2010) in prior studies. We reasoned that DHA omega-3 levels might moderate effects of PA in several ways. First, greater amounts of DHA might potentiate the effects of higher levels of PA on cognitive function. Such a finding would suggest that combining a diet high in omega-3 with a physically active lifestyle might prove more beneficial to cognitive function than either treatment by itself. However, an alternative outcome is that a deficiency in both PA and omega-3 PUFAs would result in reduced cognitive function. Such a finding might suggest that greater amounts of either omega-3 or PA could be sufficient for elevating cognitive function and that greater amounts of omega-3 could mitigate the deleterious effects of low amounts of PA.

2. Methods

2.1. Participants

Participants were middle-aged adults (30–54 years of age) recruited through the University of Pittsburgh Adult Health and Behavior (AHAB) project (Muldoon et al., 2010). A total of 1379 participants were recruited via mass mail solicitation from communities of southwest Pennsylvania. Exclusion criteria for the AHAB project included a reported history of atherosclerotic cardiovascular disease, chronic kidney or liver disease, cancer treatment in the preceding year, major neurological disorders, schizophrenia or other psychotic illness, and current pregnancy or perimenopausal menstrual irregularities. Participants were required to speak English as their primary language for at least the past 5 years. From the AHAB registry cohort of 1379 individuals, 1295 were included in the AHAB study, where subsets of participants could elect to participate in one or more additional and smaller sub-studies that included, among other measures, blood samples for fatty