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Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging

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ABSTRACT

We hypothesized that higher levels of omega-3 fatty acids, vitamin D, and physical activity relate to cortical sparing, whereas higher levels of cholesterol, systolic blood pressure, and body mass index (BMI) relate to increased atrophy in the adult lifespan. Longitudinal measures of cortical thickness were derived from magnetic resonance imaging scans acquired (mean interval 3.6 years) from 203 healthy persons aged 23–87 years. At follow-up, measures of BMI, blood pressure, and physical activity were obtained. Blood levels of docosahexaenoic acid, eicosapentaenoic acid, vitamin D, and cholesterol were measured in a subsample (n = 92). Effects were tested in cortical surface-based analyses, with sex, age, follow-up interval, and the interactions between each included as covariates. Higher levels of docosahexaenoic acid, vitamin D, and physical activity related to cortical sparing. Higher cholesterol and BMI related to increased cortical thinning. Effects were independent, did not interact with age, and the cholesterol effect was restricted to males. Eicosapentaenoic acid and blood pressure showed no effects. The observed effects show promise for potential factors to reduce cortical atrophy in normal aging.

1. Introduction

There is increasing awareness that lifestyle factors may affect neuroanatomical and cognitive outcomes across the lifespan. Also healthy aging yields cortical thinning, reduced neuroanatomical volumes, and cognitive decline (Fjell et al., 2009, 2010, 2012; Nyberg et al., 2012; Raz et al., 2010; Walhovd et al., 2011), but there is wide variability in measures of brain integrity among individuals of similar age. Whereas genetic risk factors so far may explain a small portion of the variance (Erten-Lyons et al., 2013), several lifestyle factors have been related to neuroanatomical volumes in aging (Brooks et al., 2013; Erickson et al., 2008, 2013; Scarmeas et al., 2011; Smith et al., 2010). In the present study, we investigate how markers associated with: (1) nutrient intake, specifically eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and vitamin D; (2) cardiovascular health, specifically cholesterol, and blood pressure; as well as (3) body mass index (BMI) and physical activity level, relate to longitudinal cortical atrophy in adults. These markers have not been collectively investigated in a longitudinal design to determine their common and unique influence on regional cortical thinning.

Nutritional differences have been linked to brain and cognitive outcomes at different stages of life (Helland et al., 2003; Henriksen et al., 2008; Nurk et al., 2007). Findings with regard to effects of omega-3 have been mixed. Some have found low levels to be a risk (Cederholm and Palmblad, 2010; Dangour et al., 2010; Kalmijn et al., 1997, 2004; Samieri et al., 2008), and higher levels to be protective for brain and cognition (Brenner, 2012; Samieri et al., 2012; Tan et al., 2012; Titova et al., 2012), while others have not observed an association (Devore et al., 2009; Engelhart et al., 2002). Recently, however, an omega-3 fatty acid intervention study in older adults reported improvements in brain structure and function (Witte et al., 2013). Whereas some authors have reported effects on whole brain or regionally unspecific associations (Tan et al., 2012;

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Titova et al., 2012), specific regional effects including the temporal lobe have also been found (Samieri et al., 2012; Witte et al., 2013), indicating a candidate effect site. Vitamin D deficiency has been related to cognitive function and higher risk of Alzheimer's disease (AD) (Balion et al., 2012) and magnetic resonance imaging (MRI)-indicators of cerebrovascular disease (Buell et al., 2010). However, data are lacking as to whether and which parts of the brain may be affected by vitamin D levels (Annweiler et al., 2012).

Cholesterol is assumed a mediator of brain changes in aging, but its role is uncertain, as the findings from different, mostly cross-sectional studies, are highly mixed (Kin et al., 2007; Kivipelto et al., 2002; Leritz et al., 2011; Mielke et al., 2005; Reitz et al., 2004; Solomon et al., 2009). High blood pressure is a well-known risk factor for cognitive decline and neurodegenerative disease, and has been linked to gray matter changes in normal aging (den Heijer et al., 2005; Korf et al., 2004; Leritz et al., 2011; Nagai et al., 2008; Raz et al., 2007a, 2007b), but there may be a complex and bidirectional relationship (Skoog et al., 1998). For BMI, the focus has been primarily on obesity, which is associated with increased risk for dementia (Kivipelto et al., 2005; Profenno et al., 2010), global brain volume reduction (Gunstad et al., 2008), and reduced gray matter volumes in limbic circuits, including frontal and temporal areas, and effects have also been found in parietal areas (Brooks et al., 2013; Kurth et al., 2012; Pannacciulli et al., 2006). Longitudinal investigation covering a wide span of BMIs may illuminate whether only obesity is associated with structural differences, or atrophy associations can be found as a linear effect along the full range of BMI. The focus on limbic circuits may make frontal and temporal areas especially likely effect sites. Furthermore, higher physical activity levels have been associated with higher cognitive function and lower incidence of dementia (Chang et al., 2010; Erickson et al., 2012; Laurin et al., 2001). Besides effects on hippocampal volume (Erickson et al., 2011), studies have especially found effects of physical activity and exercise on frontal gray matter volumes (Colcombe et al., 2006; Weinstein et al., 2012). However, general physical activity level may in principle affect brain changes more widely (Erickson et al., 2013), for example via cardiovascular mechanisms. There is a need to investigate to what extent effects of physical activity interact with effects of BMI, or relate to effects of other lifestyle factors on cortical structure.

We hypothesize that some life style factors will be protective and yield cortical sparing, whereas others represent risks yielding accelerated atrophy in aging. Based on the previously reviewed research, likely effect sites for some factors can be suggested, whereas for others, only a direction of effect is hypothesized as: (1) higher levels of omega-3 fatty acids and vitamin D will be related to temporal lobe cortical sparing; (2) higher cholesterol and systolic blood pressure will be associated with more atrophy; (3) higher BMI will be associated with more frontal and temporal atrophy; and (4) higher level of physical activity will be associated with less atrophy, especially in frontal areas. The extent to which these effects may be unique or interdependent, and whether they will interact with age and sex, is unknown, and will also be investigated in a retrospective study of these markers in participants who had 2 brain scans on average 3.6 years apart.

2. Methods

2.1. Sample

The longitudinal sample was drawn from the ongoing project *Cognition and Plasticity through the Lifespan* at the University of Oslo (Fjell et al., 2008; Westlye et al., 2010), approved by the Regional Ethical Committee of Southern Norway. Written consent was obtained from all participants. Participants were recruited through newspaper ads. At both time points (Tp1, Tp2), participants were screened with health interviews. Participants were required to be right handed, fluent Norwegian speakers, and have normal or corrected to normal vision and hearing. Exclusion criteria were history of injury or disease known to affect central nervous system (CNS) function, including neurologic or psychiatric illness or serious head trauma, being under psychiatric treatment, use of psychoactive drugs known to affect CNS functioning, and MRI contraindications. Participants were required to score $\geq$26 on the Mini Mental State Examination (MMSE; Folstein et al., 1975), have a Beck Depression Inventory (Beck and Steer, 1987) score $\leq$16, and obtain a normal IQ or above ($\geq$85) on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). At follow-up, an additional set of inclusion criteria was employed: MMSE change from Tp1 to Tp2 $<$ 10%; California Verbal Learning Test II—Alternative Version (CVLT II; Delis et al., 2000) immediate delay and long delay T-score $>$ 30; CVLT II immediate delay and long delay change from Tp1 to Tp2 $<$ 60%. At both time points scans were evaluated by a neuroradiologist and required to be deemed free of significant injuries or pathologic conditions.

Two hundred eighty-one participants completed Tp1 assessment. For the follow-up study, 42 opted out, 18 could not be localized, 3 did not participate because of undisclosed health reasons, and 3 had MRI contraindications, yielding a total of 66 dropouts. Independent samples t tests revealed that dropouts had significantly lower full-scale intelligence quotient ($t = -3.92$, $p < 0.001$) and Beck Depression Inventory ($t = -2.02$, $p = 0.046$) scores but comparable CVLT and MMSE scores. Of the 215 participants who completed MRI and neuropsychological testing at both time points, 8 failed to meet additional inclusion criteria for the follow-up described previously. This resulted in a follow-up sample of 207 participants of whom 4 had no measures for BMI, blood pressure, or blood biomarkers (see the following), and were excluded from the final analyses. The final sample for the current analyses included n = 203 in the age range 23–87 years, and for 92 (90 among the 203, plus 2 of the 207 satisfying criteria but lacking the BMI measure), blood biomarkers measures were available. Please see Table 1 for descriptive details for the full sample and subsample.

2.2. MRI acquisition and processing

Imaging data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions; Erlagen, Germany) at Rikshospitalet, Oslo University Hospital. The pulse sequence used for morphometric analyses were 2 repeated 160 slices sagittal T_1-weighted magnetization prepared rapid gradient echo sequences with the following parameters: repetition time/echo time/time to inversion/flip angle = 2400 ms/3.61 ms/1000 ms/8°, matrix = 192 × 192, field of view = 240, voxel size = 1.25 × 1.25 × 1.20 mm per participant per visit. To increase the signal-to-noise ratio the 2 runs were averaged during pre-processing at both time points. Scanning time for each magnetization prepared rapid gradient echo sequence was 7 minutes 42 seconds.

The raw data were reviewed for quality, and automatically corrected for spatial distortion because of gradient nonlinearity (Jovicich et al., 2006) and B_1 field inhomogeneity (Sled et al., 1998). The two image volumes collected at each time point were co-registered, averaged to improve the signal-to-noise ratio, and resampled to isotropic 1-mm voxels. Images were first processed cross-sectionally (independently) for each time point with the FreeSurfer software package (version 5.1.0; Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA. http://surfer.nmr.mgh.harvard.edu/). This processing includes motion correction, removal of nonbrain tissue, automated Talairach transformation, intensity correction, volumetric segmentation (Fischl et al., 2002),