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Vascular risk factors, cerebrovascular reactivity, and the default-mode brain network

Thaddeus J. Haight [a,*], R. Nick Bryan [b], Guray Erus [b], Christos Davatzikos [b], David R. Jacobs [c], Mark D'Esposito [d], Cora E. Lewis [e], Lenore J. Launer [a]

[a] Laboratory of Epidemiology and Population Sciences, National Institute on Aging, 7201 Wisconsin Avenue, Room 3C309, Bethesda, MD 20814, USA
[b] Department of Radiology, University of Pennsylvania, 3600 Market St., Philadelphia, PA 19104, USA
[c] Division of Epidemiology and Community Health, University of Minnesota, 1300 S. 2nd Street, Suite 300, Minneapolis, MN, USA
[d] Helen Wills Neuroscience Institute, University of California-Berkeley, 132 Barker Hall, Berkeley, CA, USA
[e] Department of Medicine, Division of Preventive Medicine, University of Alabama, Medical Towers 614, 1717 11th Avenue South, Birmingham, AL, USA

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ABSTRACT

Cumulating evidence from epidemiologic studies implicates cardiovascular health and cerebrovascular function in several brain diseases in late life. We examined vascular risk factors with respect to a cerebrovascular measure of brain functioning in subjects in mid-life, which could represent a marker of brain changes in later life. Breath-hold functional MRI (fMRI) was performed in 541 women and men (mean age 50.4 years) from the Coronary Artery Risk Development in Young Adults (CARDIA) Brain MRI sub-study. Cerebrovascular reactivity (CVR) was quantified as percentage change in blood-oxygen level dependent (BOLD) signal in activated voxels, which was mapped to a common brain template and log-transformed. Mean CVR was calculated for anatomic regions underlying the default-mode network (DMN) – a network implicated in AD and other brain disorders – in addition to areas considered to be relatively spared in the disease (e.g. occipital lobe), which were utilized as reference regions. Mean CVR was significantly reduced in the posterior cingulate/precuneus ($\beta = -0.063$, 95% CI: -0.106, -0.020), anterior cingulate ($\beta = -0.055$, 95% CI: -0.101, -0.010), and medial frontal lobe ($\beta = -0.050$, 95% CI: -0.092, -0.008) relative to mean CVR in the occipital lobe, after adjustment for age, sex, race, education, and smoking status, in subjects with pre-hypertension/hypertension compared to normotensive subjects. By contrast, mean CVR was lower, but not significantly, in the inferior parietal lobe ($\beta = -0.024$, 95% CI: -0.062, 0.014) and the hippocampus ($\beta = -0.006$, 95% CI: -0.062, 0.050) relative to mean CVR in the occipital lobe. Similar results were observed in subjects with diabetes and dyslipidemia compared to those without these conditions, though the differences were non-significant. Reduced CVR may represent diminished vascular functionality for the DMN for individuals with prehypertension/hypertension in mid-life, and may serve as a preclinical marker for brain dysfunction in later life.

Introduction

Changes in brain functioning in mid-life, before structural changes in the brain, may represent an important marker of future brain health in later life (Alsop et al., 2010; Bendlin et al., 2010). Vascular risk factors (VRF) and vascular disease have been shown to be associated with reduced cerebrovascular function (e.g., cerebral blood flow) (Claus et al., 1998; Riecker et al., 2003; Wu et al., 2008; Jagust and D'Esposito, 2009). In addition, cerebrovascular disorders – e.g., cerebral small vessel disease, white matter lesions, and reduced white matter integrity – have been linked to reduced brain network functioning that include the default-mode network (DMN) and other networks involved in cognitive control (Damoiseaux and Greicius, 2009; Mayda et al., 2011; Papma et al., 2013). Evidence from epidemiologic studies of VRF in mid-life and risk of dementia in late-life (Launer et al., 1995, 2000; Kivipelto et al., 2001; Roberts et al., 2014), as well as cumulating evidence of neurovascular mechanisms of Alzheimer's disease (AD) (Benarroch, 2007; Novak, 2012) warrants investigation of VRF and brain changes that could represent vascular contributions to AD.

The DMN represents a resting state network that consists of a set of brain regions that co-activate when subjects are at rest, and deactivate together when subjects become engaged in external cognitive tasks (e.g., episodic learning) (Raichle et al., 2001; Daselaar et al., 2004; Sperling, 2007; Buckner et al., 2008; Miller et al., 2008). Studies of brain network dysfunction, using blood-oxygen level dependent functional MR imaging (BOLD fMRI), have implicated the DMN as one of the central representative networks in aging and AD pathophysiology

* Corresponding author.
E-mail address: tad.haight@nih.gov (T.J. Haight).

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(Greicius et al., 2004; Hedden et al., 2009; Brier et al., 2014). These studies have shown that DMN disconnectivity could represent a biomarker for preclinical AD (Greicius et al., 2004; Hedden et al., 2009; Sheline and Raichle, 2013; Brier et al., 2014) as well as a marker of AD progression (Damoiseaux et al., 2012). Evidence from previous studies has implicated vascular changes in DMN disruption (Damoiseaux and Greicius, 2009; Mayda et al., 2011; Papma et al., 2013). Additionally, reduced cerebrovascular function (e.g., cerebral blood flow) has been observed in brain regions that overlap DMN regions (e.g., parietal cortex) in individuals with AD (Alsop et al., 2000; Johnson et al., 2005; Dai et al., 2009; Jagust and D'Esposito, 2009; Schuff et al., 2009; Stefani et al., 2009) mild cognitive impairment (MCI) (Johnson et al., 2005; Duschek and Schandry, 2007) as well as cognitively healthy older adults(Claus et al., 1998; Wu et al., 2008; Jagust and D'Esposito, 2009).

Cerebrovascular reactivity (CVR) represents a measure of vascular responsiveness, based on vasodilation of cerebral vessels, given induced changes in the brain (e.g., increased CO_2) that can occur during given physical states (e.g., breath-hold) (Kastrup et al., 1999, 2001; Handwerker et al., 2007). Typically, CVR has been used to evaluate global brain response (Last et al., 2007; Jagust and D'Esposito, 2009) as well as to measure effects on hemodynamic response in specific vascular territories (Vernieri et al., 1999; Silvestrini et al., 2000; Sorond et al., 2010). However, regional differences in CVR have been observed (Kastrup et al., 1999) and, additionally, CVR has been shown to vary regionally with respect to VRF (Novak, 2012). It is possible that reduced CVR—i.e., representative of lower cerebrovascular function associated with different VRF—may occur in brain regions that underlie the DMN and may affect DMN function.

We hypothesize that for adults in midlife reduced CVR, associated with VRF (e.g., hypertension, diabetes, dyslipidemia), occurs in regions of the brain that underlie the DMN, and could reflect reduced vascular functionality in the network. Furthermore, we hypothesize that reduced CVR occurs simultaneously in the hippocampus, which has a functional relationship with the DMN (i.e., the hippocampus activates while the DMN deactivates during learning tasks). Reduced CVR in these regions could represent changes in vascular brain function for individuals with VRF in mid-life, and could represent a preclinical marker of brain health in later life.

Materials and methods

Study sample

Participants were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a longitudinal study to investigate the determinants and development of cardiovascular disease in young adults. Details of the recruitment of the study sample are available (Friedman et al., 1988). Of the 5115 adults enrolled in the study, 3499 (72% of survivors) were evaluated at the 25-year follow-up exam. As part of this exam, a sub-sample was invited to participate in the CARDIA brain sub-study. This study recruited subjects from 3 of the 4 CARDIA field centers, and was designed to investigate the morphology, pathology, physiology and function of the brain with magnetic resonance imaging (MRI) technology. Exclusion criteria at the time of sample selection, or at the MRI site, were a contraindication to MRI or a body size that was too large for the MRI scanner. Of those who were eligible for the sub-study, our target was scans in 700 individuals; we obtained 719 individuals, who received MRI scans.

All participants provided written informed consent at each exam, and institutional review boards from each field center and the coordinating center annually approved the CARDIA study. Separate participant written consent for participation in the CARDIA brain sub-study was obtained, and separate approval was given by the IRBs of the participating sites and the IRB covering Intramural Research at the National Institute on Aging (NIA).

MRI acquisition and processing

MRI scans were obtained for patients using 3-T MR scanners located proximal to each CARDIA clinical site. Details of the scanners used, training of MRI technologists at the different sites, implementation of study protocols, and quality assurance of scanner stability and performance are provided elsewhere (Launer et al., 2015). A 40-minute scan protocol was implemented and a prioritized order of brain sequences was obtained. For participant safety, scans were examined initially by the MR technician. Any detection of pathology or other medical abnormalities were reported to the site PI and radiologist immediately and appropriate steps were taken. Otherwise, each site followed standard operating procedures that involved reading of the scan within 48 h.

Post-scan image processing was performed by the Section of Biomedical Image Analysis (BIA), Department of Radiology, University of Pennsylvania. An initial QC protocol identified any motion artifacts or any other quality issues. Subjects that failed this QC test were flagged for inspection. After this inspection, an automated pipeline was applied on the scans. Quality checks were performed on intermediate and final processing steps by visual inspection and by identification of outliers of calculated variable distributions.

MRI measures

According to previously described methods (Goldszal et al., 1998; Shen and Davatzikos, 2002; Lao et al., 2008; Zacharaki et al., 2008), an automated computer algorithm was used to segment MRI structural images of supratentorial brain tissue into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). GM and WM were further characterized as normal and abnormal tissue, and assigned as 92 anatomic regions of interest (ROIs) in each hemisphere. These 92 anatomic regions comprise the Jakob atlas (Kabani et al., 1998), which was used as a brain template to which the MRI brain measures were co-registered.

Based on previous reports (Buckner et al., 2008; Hedden et al., 2009), and the Jakob atlas available in the current study, a priori defined brain regions were selected to investigate the DMN. Regions, and corresponding subregions, included: posterior cingulate/precuneus (PCC); inferior parietal lobe (angular gyrus and supramarginal gyrus) (INF); anterior cingulate (ACC); and medial frontal lobe (MFL). In addition, although the hippocampus is not part of the DMN, it was selected as a region of interest given its functional relationship with the DMN (i.e., the hippocampus activates while the DMN deactivates during learning tasks) (Sperling, 2007; Miller et al., 2008; Jagust and D'Esposito, 2009). As a reference for comparison throughout the study, we selected the occipital lobe (i.e., occipital pole and superior, middle, and inferior occipital gyri) and sensorimotor cortex (i.e., precentral gyrus, postcentral gyrus), which are thought to be less vulnerable to disease (e.g., AD) (Thompson et al., 2001; Resnick et al., 2003; Yakushev et al., 2008). In addition, other cortical brain regions (i.e., excluding those representative of the DMN, hippocampus, occipital and sensorimotor cortex) were used to represent Non-DMN regions.

Cerebrovascular reactivity (CVR)

CVR acquisition

Each participant performed a breath-hold task during acquisition of BOLD fMRI. We used a block design with two interleaved conditions. Subjects received a visual instruction, while in the scanner, to breathe normally for 30 s; then hold their breath after expiration for 16 s; then resume normal breathing. This procedure was repeated 4 times in succession, and the recorded measurements were averaged for the 4 repetitions. The BOLD scans were corrected for motion and smoothed. This step was followed by a general linear model (GLM) analysis, for each subject, where the time course in BOLD signal at each voxel was fit with: 1) a regressor representative of the interleaved block-design, or block-model; and 2) a 9 second delay in the block-model to account