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Fasting plasma insulin and the default mode network in women at risk for Alzheimer's disease

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Abstract

Brain imaging studies in Alzheimer's disease research have demonstrated structural and functional perturbations in the hippocampus and default mode network (DMN). Additional evidence suggests risk for pathological brain aging in association with insulin resistance (IR). This study piloted investigation of associations of IR with DMN-hippocampal functional connectivity among postmenopausal women at risk for Alzheimer's disease. Twenty middle-aged women underwent resting state functional magnetic resonance imaging. Subjects were dichotomized relative to fasting plasma insulin levels (i.e., > 8 μIU/mL [$n = 10$] and < 8 μIU/mL [$n = 10$]), and functional connectivity analysis contrasted their respective blood oxygen level-dependent signal correlation between DMN and hippocampal regions. Higher-insulin women had significantly reduced positive associations between the medial prefrontal cortex and bilateral parahippocampal regions extending to the right hippocampus, and conversely, between the left and right hippocampus and medial prefrontal cortex. Neuropsychological data (all within normal ranges) also showed significant differences with respect to executive functioning and global intelligence. The results provide further evidence of deleterious effects of IR on the hippocampus and cognition. Further imaging studies of the IR-related perturbations in DMN-hippocampal functional connectivity are needed.

Keywords: Default mode network; Hippocampus; Insulin resistance; Postmenopausal women; Risk for Alzheimer's disease; Functional connectivity

1. Introduction

Increasing age is associated with functional decline in a variety of internal organ systems, including the brain (Tomasi and Volkow, 2012), and cognitive decline is a common and critical complaint among aging individuals (Deary et al., 2009). Greater understanding of risk factors associated with pathological brain aging, particularly Alzheimer's disease (AD), may lead to interventions for the treatment, and possibly the prevention, of dementia.

Individual factors that appear to affect risk for decline include nonmodifiable characteristics, such as genetic factors and family history of disease, and modifiable factors, which include metabolic functioning, body weight, and cardiovascular disease (Barnes and Yaffe, 2011). One of the modifiable risk factors for aging-related decline is the state of insulin resistance (IR), which is the main pathological condition underlying vascular disorders, such as type 2 diabetes, and cardiovascular disease, and occurs when the body becomes less responsive to insulin for the maintenance of normal blood glucose levels (Reaven, 1988). Cumulative data on the associations of IR and IR-related states ("metabolic syndrome," type 2 diabetes) suggest considerable pathological effects on the aging brain (Bosco et al., 2011; Reagan, 2007). There may be critical interactions that occur between modifiable and nonmodifiable risk factors for decline in function. Given that glucose dysregulation can be modified with pharmacologic and behavioral interventions,

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the goal of improving metabolic functioning in aging individuals may prove to be a prudent and novel means of preventive care for aging-related cognitive decline.

Intervention research in aging populations may benefit from clinical investigations of the hippocampus and its functionally connective brain regions. There are wide, deleterious implications of hippocampal atrophy and alterations in its function (Dickerson and Sperling, 2008; Rasgon et al., 2011). The medial temporal lobe region, particularly the hippocampus, is especially rich in insulin receptors, and significant evidence suggests deleterious effects of IR and diabetes on hippocampal morphology (den Heijer et al., 2003; Hempel et al., 2012; Rasgon et al., 2011) and hippocampal-mediated cognitive domains, such as verbal memory, attention, and executive function (Rasgon et al., 2011). We recently reported significant negative association of IR and hippocampal morphology (Rasgon et al., 2011), similar to previous reports of greater temporal lobe atrophy in association with IR among diabetic and nondiabetic populations (den Heijer et al., 2003; Hempel et al., 2012). Our data also suggested negative effects of IR on cognitive performance (Rasgon et al., 2011), which is in line with the cumulative data showing worse cognitive performance in diabetics (Kodl and Seaquist, 2008). To our knowledge, no studies to date have examined IR with respect to functional connectivity in the brain.

Pioneering work by a number of investigators has established the importance of the default mode network (DMN), or "resting state," as a biomarker of cognitive function and aging-related decline (Greicius et al., 2004; Sorg et al., 2007; Zhou et al., 2010). Indeed, the DMN has been proven to be a robust correlate of pathological brain aging (Zhou et al., 2010). It encompasses widely separate brain regions, including the medial prefrontal cortex (MPFC), the posterior cingulate cortex (PCC), and lateral parietal cortices, all of which display a high degree of functional connectivity during rest (Fox et al., 2005). The DMN essentially "deactivates" during mental tasks with moderate or greater cognitive demand and "activates" during mental rest with eyes closed (Fox et al., 2005). Utilizing functional connectivity analysis allows the opportunity to examine DMN connections with critical brain regions, such as the hippocampus. Connectivity between these brain regions, in particular, may be especially important given the significance of the hippocampus for memory and dementia (Wang et al., 2010). The present study sought to further investigate the role of IR in risk for pathological brain aging by utilizing a contrast analysis of functional connectivity between the DMN and the hippocampus during rest using functional magnetic resonance imaging (MRI) in a sample of healthy postmenopausal women at risk for dementia.

2. Methods

2.1. Study participants and screening procedures

The sample consisted of a sample of 20 physically healthy, cognitively-intact Caucasian women at risk for AD, all of whom were participants in a larger National Institutes of Health-funded study of brain function during postmenopause (R01 AG22008 to N. Rasgon). In the umbrella study protocol, risk factors for AD were the presence of at least 1 apolipoprotein E (APOE) 4 allele, a first-degree relative with AD, and/or a personal history of recurrent major depressive disorder. All subjects with a history of depression were required to be euthymic for at least 1 year prior to in-person screening. Baseline brain imaging (MRI and positron emission tomography) and neuropsychological data from the larger study sample have been published (Silverman et al., 2011; Wroolie et al., 2011). The resting state brain imaging protocol conducted in the present pilot study was initiated midway through subject recruitment in the larger study. These subjects did not appear to differ from the larger sample with respect to any demographic or clinical characteristics, which are fully summarized in Table 1. The cognitive test battery, which consisted of measures considered to assess verbal and nonverbal cognitive function, as well as measures of general cognitive functioning, included the following tests: Auditory Consonant Trigrams (Milner, 1972), Benton Visual Retention Test (Benton et al., 1983), Buschke-Fuld Selective Reminding Test (Buschke and Fuld, 1974), Color Trail Making Test (D'Elia and Satz, 1993), Delis Kaplan Executive Function System Color-Word and Verbal Fluency Tests (Delis et al., 2001), Rey-Osterrieth Complex Figure Test (Osterrieth, 1944; Rey, 1941), vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (The Psychological Corporation, 1999), Wechsler Adult Intelligence Scale-Third Edition (The Psychological Corporation, 1997), and Wechsler Memory Scale-Third Edition (The Psychological Corporation, 2002). In the larger study, neuropsychological data were analyzed using a priori clustering of *Z*-score transformed performance variables from across the test battery reflecting the cognitive domains of executive function, verbal memory, visual memory, and attention/processing speed (please see Wroolie et al., 2011 for further data). This approach reduced type 1 errors due to multiple comparisons.

Per the larger study protocol, other study inclusion/exclusion criteria were a minimum education level of 8 years of education; adequate visual and auditory acuity to allow neuropsychological testing; no history of significant cognitive decline, vascular disease, Parkinson's disease, transient ischemic attacks, carotid bruits, or lacunes on MRI scan, myocardial infarction, unstable cardiac disease, significant cerebrovascular disease, uncontrolled hypertension (systolic blood pressure $>$ 170 mm Hg or diastolic blood pressure $>$ 100 mm Hg), history of significant liver disease, clinically significant pulmonary disease, or cancer; no major mood episode in the past 12 months or a score of $>$ 8 on the 17-item Hamilton Depression Rating Scale; no history of major mental illness (excluding mood disorders); no history of drug or alcohol abuse; no contraindication for MRI scan