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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 IU/mL [*n* 10] and 8 IU/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

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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, 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 agingrelated 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.

Methods

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 ColorWord and Verbal Fluency Tests (Delis et al., 2001), ReyOsterrieth 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 (e.g., metal in body, claustrophobia). Participants were also excluded if they used any medications with the potential to significantly affect psychometric test results, including centrally active -blockers, narcotics, clonidine, antiparkinsonian medications, antipsychotics, systemic corticosteroids, medications with significant cholinergic or anticholinergic effects, anticonvulsants, warfarin, or sporadic use of phytoestrogen-containing products, which may produce estrogen-like agonist and antagonist effects (Silverman et al., 2011; Wroolie et al., 2011).

The study in its entirety was approved by the Stanford University Institutional Review Board and all participants provided written informed consent. Per study protocol, all subjects underwent a series of assessments, including MRI, neuropsychological testing, genotyping for APOE, and measurement of morning fasting plasma insulin (FPI) and glucose, body weight, and height at baseline. The neuropsychological test battery assessed the domains of executive function, verbal memory, visual memory, and attention, as well as general intelligence (previously published [Wroolie et al., 2011]). General intelligence was estimated using the Wechsler Abbreviated Scale of Intelligence (The Psychological Corporation, 1999). To allow group contrast in the analysis of functional connectivity between the DMN and hippocampus, the sample was dichotomized into 2 groups by a median split of FPI level: subjects with higher insulin had FPI levels 8.71 IU/mL (group mean 13.2 6.4 IU/mL) (mean, SD, and range), while those with lower insulin had FPI levels 7.2 IU/mL (group mean 5.7 1.9 IU/mL). We note that the FPI values of subjects in the current sample were similar to previous investigations of healthy middle-aged and older adults, such as the National Health and Nutrition Examination Surveys (Wildman et al., 2008). In addition to group contrast in the functional connectivity analysis, the groups were also compared with respect to performance on neuropsychological tests of major cognitive domains (e.g., verbal memory, executive performance, and attention) using *t* tests and analysis of covariance.

Image acquisition

Imaging-related procedures were performed at the Veterans Affairs Palo Alto Healthcare System Radiological Services Facility, using a 1.5 T Signa LX (GE Medical Systems, Milwaukee, WI, USA). Functional MRI (fMRI) data were acquired using whole-brain imaging with a T2*sensitive gradient echo spiral in/out pulse sequence (repetition time 2000 ms, echo time 40 ms, flip angle 80°, field of view 240 mm, voxel-size 3.75 3.75 4.5 mm, 1 mm skip, 24 slices collected in ascending order, anterior and posterior commissure aligned, 261 temporal frames). The total duration of the fMRI scan was 8:42 minutes, during which subjects were told to rest quietly with their eyes closed. Three-dimensional high-resolution anatomical scans were acquired using a spoiled gradient echo pulse sequence (repetition

time 9.0 ms, echo time 1.9 ms, flip angle 15°, field of view 250 mm, voxel-size 0.98 0.98 1.5 mm, 2-NEX (number of excitations) scans, 124 coronal T1weighted images).

fMRI data processing and analyses

FMRI data preprocessing was conducted using SPM8 (publically available from the Wellcome Trust Centre for Neuroimaging at www.fil.ion.ucl.ac.uk/spm/software/spm8/), which included slice-time correction (ascending), temporal realignment, spatial normalization to Montreal Neurological Institute standard space using high-resolution segmented structural gray matter images and spatial smoothing with an 8-mm isotropic Gaussian filter. Quality control was performed using in-house tools available on SPM Extensions (www.fil.ion.ucl.ac.uk/spm/ext/). Functional connectivity analysis was performed using the Functional Connectivity Toolbox (www.nitrc.org/projects/conn). These data were band-pass filtered (0.008–0.09 Hz), corrected for physiological noise and motion using a CompCor strategy. Regions of interest (ROIs) were defined as 10-mm spheres of MPFC, PCC, and left and right lateral parietal cortices (LPC) where the centers were derived from Fox et al. (2005) and implemented in the toolbox. Left and right hippocampus ROIs were derived from the Automated Anatomical Labeling Atlas (TzourioMazoyer et al., 2002). Primary analysis focused on the functional connectivity between the DMN seed regions and the left and right hippocampal regions, and conversely left and right hippocampal seeds and the DMN regions. ROIto-whole-brain analyses were performed. Using the Functional Connectivity Toolbox, a full-factorial modeling was conducted on either each of the DMN nodes, or each of the hippocampal nodes, depending on the target analysis, with a contrast of [left and right lateral parietal cortices, MPFC, PCC] [1 1 1 1] of [left hippocampus, right hippocampus] [1 1]. For between group analyses, we modeled the 2 groups (higher insulin, lower insulin) and examined the interaction effects. A statistical threshold of p 0.01 for voxel height and p 0.05 false discovery rate-corrected for cluster extent were used.

Results

Demographic and clinical characteristics of the 20 subjects are presented in Table 1. All subjects were within the normal range for cognitively intact persons of their same age and educational level with respect to Mini Mental State Examination score. Dichotomized subject groups (higher- and lower-insulin) did not differ with respect to any demographic or clinical variables, with the exception of body mass index and FPI. Neuropsychological performance was within normal limits across subjects (see Wroolie et al., 2011 for complete battery for the cognitive domains of verbal memory, visual memory, and attention). However, subtle yet statistically significant differences were seen between the contrast groups with respect to the domain of executive function. Wechsler Abbreviated Scale of Intelligence scores also differed between groups. It was noted that all sample and withingroup means indicated higher-than-average general intelligence across subjects (see Table 1).

Initial functional connectivity analysis showed the expected positive associations among the main DMN nodes, i.e., the MPFC, PCC, bilateral LPC, as well as reciprocal positive

associations between the left and right hippocampal regions using 1-sample *t* tests within each group (higher and lower insulin) (*p* 0.01 corrected; Figs. 1A and 2, and Table 2). Two-sample *t* tests showed that subjects with higher insulin levels exhibited significantly reduced positive associations between the MPFC seed and left and right parahippocampal regions, and conversely, between both the left and right hippocampal seed regions and the MPFC region, relative to subjects with lower insulin levels (Fig. 2, Table 2). Functional connectivity of the PCC and LPC with the hippocampal regions did not differ between groups. Results showed that subjects with higher insulin exhibited significantly reduced positive associations between the MPFC seed and left and right parahippocampal regions, and conversely, between both the left and right hippocampal seed regions and the MPFC region (Fig. 2, Table 2). Functional connectivity of the PCC and LPC with the hippocampal regions did not differ between groups.

Further functional connectivity analysis aimed to explore the potential confounding effects of group differences in IQ and executive function on the significant brain regions initially identified. Results showed significant main effects of insulin group on MPFC-hippocampal connectivity even when controlling for IQ (*r* 0.724, *p* 0.001 and *r* 0.748, *p* 0.001, respectively). In analyses conducted for confirmatory purposes, correlations of the MPFC-hippocampal connectivity and FPI values in the group as a whole were observed to be much stronger (left hippocampus: *r* 0.735, *p* 0.001; right hippocampus: *r* 0.802, *p* 0.001), than connectivity with IQ (left hippocampus: *r* 0.321, *p* 0.168; right hippocampus: *r* 0.428, *p* 0.060) or executive function (left hippocampus: *r* 0.440, *p* 0.052; right hippocampus: *r* 0.538, *p* 0.014).

Discussion

The current study presents, to our knowledge, the first report on effects of the modifiable AD risk factor, IR, on DMN functional connectivity among middle-aged women at risk for AD. The present findings of disrupted DMN-hippocampal functional connectivity add to our previously reported findings of hippocampal atrophy and worse cognition in association with increasing degree of IR (Rasgon et al., 2011). DMN connectivity with the hippocampal region may be especially important in individuals at risk for AD, given the association of the DMN with episodic memory and visuospatial imagery in patients with AD (Zhou et al., 2010). While we can only speculate, pending further data, we suggest that IR acts as a moderating variable in individuals at risk for AD, acting as a catalyst for deleterious brain morphology and network connectivity. Further, our results extend cumulative empirical investigations of DMN activity in individuals with specific risk factors for AD, of which APOE4 is the most studied nonmodifiable risk factor for AD and in itself is associated with alterations in DMN activity in both older individuals (Brown et al., 2011; Greicius et al., 2004; Machulda et al., 2011; Sheline et al., 2010) and young adults (Filippini et al., 2009).

The DMN has been investigated in a number of different subject populations and disease models as a biomarker of brain function. Decreased DMN activity has been demonstrated in patients with AD (Greicius et al., 2004) and in older individuals at risk for AD carrying the APOE -4 allele (Sorg et al., 2007). Further, disrupted DMN activity has been differentially demonstrated in AD compared with other dementias (Zhou et al., 2010). Our present results

add to the increasing evidence that perturbation in the functional connectivity of DMN brain regions with the hippocampus may be an early indicator of pathological aging-related decline in brain function. For example, a study by Fleischer and colleagues (Fleisher et al., 2009) compared older cognitively-intact individuals at increased risk for AD (by APOE4 and family history of AD) and matched controls not at risk for AD, and demonstrated greater distinction between groups during resting state analysis compared with encodingassociated fMRI techniques. Supporting data by Wang and colleagues strongly suggest significant cognitive mediating effects of DMN connectivity with the hippocampus (Wang et al., 2010). Further, Hedden et al. (2009) have reported data showing that -amyloid deposition, a well-established, potentially modifiable biomarker for AD in the presence of APOE4 genotype, to be associated with reduced DMN-hippocampal connectivity in clinically normal older adults. Taken together, AD-related dysfunction in connectivity of these key brain regions may be critical areas for further investigation and therapeutic targeting.

It is possible that several cumulative risk factors for AD (both modifiable and nonmodifiable) are associated with altered hippocampal functioning in association with the DMN. IR, sometimes called “prediabetes,” is the underlying metabolic condition of type 2 diabetes, and can be corrected with pharmacologic and behavioral treatments. Recent data have shown differential functional connectivity of the DMN in type 2 diabetes (Zhou et al., 2010), which is itself associated with a significant increase in AD (Luchsinger, 2010). Earlier data from Convit and colleagues indicated negative effects of increasing glucose intolerance and hippocampal volume and verbal recall among elderly and middle-aged men and women (Convit et al., 2003). More recently, Hempel and colleagues reported greater hippocampal atrophy among women with diabetes or biomarkers of glucose dysregulation compared with women with normal glucose and men (Hempel et al., 2012). Our current results, along with our previously published findings of hippocampal atrophy in association with IR, point to the importance of clinically addressing IR in aging individuals.

There are certain limitations to our results. The main limitation is its sample size, which precluded analysis of interactions, such as the potential influence of APOE4. At the same time, the sample is noteworthy for its homogeneity. All subjects were middle-aged cognitively normal, euthymic women at risk for AD, users of hormone therapy, and APOE4 was equally represented between the 2 groups. The functional connectivity differences observed between higher and lower insulin groups may have been augmented by the subtle yet statistically significant differences in executive function and IQ observed between the 2 groups. However, it is noteworthy that all subjects tested within normal limits on all neuropsychological tests. Further, exploratory analysis using the Functional Connectivity Toolbox showed much stronger associations of functional connectivity in relation to IR as compared with associations in relation to executive function or IQ. Lastly, the study is limited by its use of a proxy biomarker of IR (FPI), rather than 1 of the gold standard measures of IR in nondiabetic individuals—the insulin suppression test and the hyperinsulinemic euglycemic clamp (Reaven, 1988). However, surrogate biomarkers of IR, such as FPI and/or the homeostatic model assessment of insulin resistance (HOMA-IR, which is largely driven by FPI), are highly correlated with the insulin clamp measures of IR (Matthews et al., 1985; Vague and Nguyen, 2002), while being inexpensive and easy to

measure in clinical populations. As future research unfolds, our understanding of IR and brain aging would benefit from additional investigation on the independent effects, and epigenetic interactions, of modifiable and nonmodifiable risk factors for AD.

In summary, these preliminary results suggest specific perturbation in DMN functional connectivity with the hippocampus. The data also lend further support to the importance of IR as a biomarker for risk of pathological brain aging. Toward the goal of preventing or slowing the progress of AD, investigations of DMN activity in relation to modifiable AD risk factors, such as IR, have the potential to greatly inform clinical treatment of pathological aging and may prove useful in the identification of AD-associated pathological aging. Further investigation may explore the potential utility of DMN activity and IR as concurrent biomarkers for pathological brain aging.

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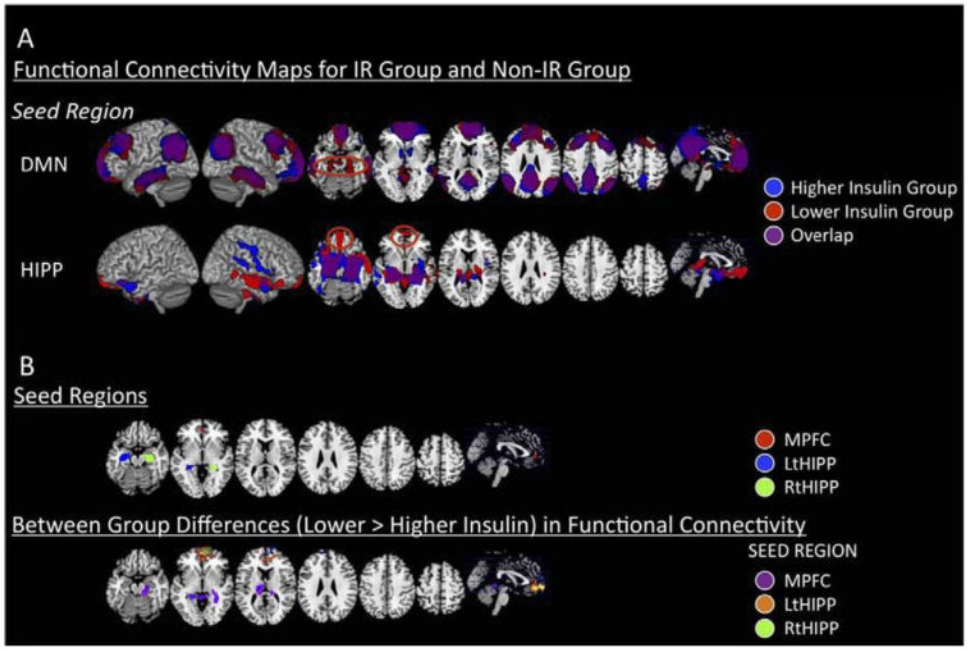

Fig. 1.

Functional connectivity maps for the higher insulin and lower insulin contrast groups. (A) Brain regions that showed positive association with seed regions' time series. Seeds were placed in the default-mode network (DMN) (medial prefrontal cortex [MPDF], posterior cingulate cortex [PCC], left and right lateral parietal cortices [LtLPCand RtLPC, respectively]) and left and right hippocampi (LtHIPP and RtHIPP). Weighted average of the 4 seed regions for the DMN and 2 seed regions for the HIPP are shown in this figure (p 0.01 whole-brain corrected). Maps of each individual seed region are shown. Red circles indicate brain regions that show activation in the lower insulin group (red) but not the higher insulin group (blue), and are in the medial prefrontal and hippocampal regions. (B) Between group differences in functional connectivity. Upper panel: Seed regions where their functional connectivity maps show significant difference between groups. Lower panel: Compared with the lower insulin group, higher-insulin subjects showed significantly reduced positive associations between medial prefrontal cortex (MPFC) seed and bilateral hippocampal regions (pink-purple) as well as reduced positive associations between LtHIPP seed and medial prefrontal region (orange-yellow) and RtHIPP seed and medial prefrontal region (blue-green) (p 0.01 whole-brain corrected).

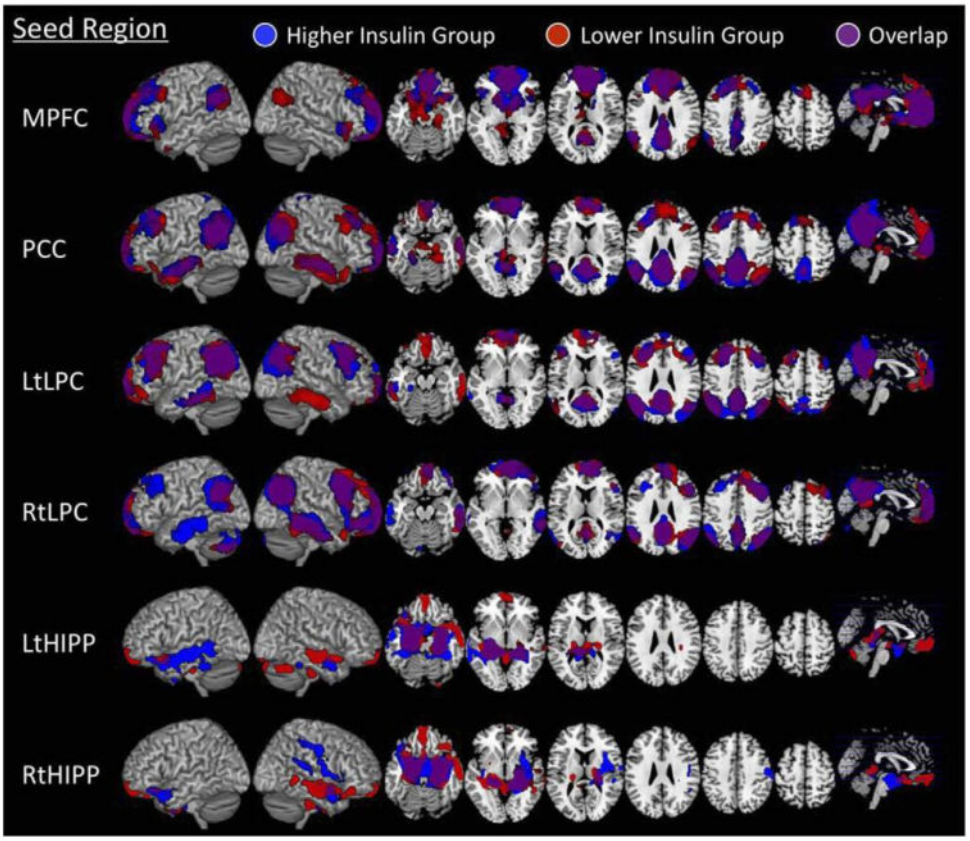

Fig. 2.

Functional connectivity maps for the higher insulin and lower insulin groups. Brain regions that show positive association with seed regions' time series. Seeds were placed in the default-mode network (DMN) (medial prefrontal cortex [MPFC], posterior cingulate cortex [PCC], left and right lateral parietal cortices [LtLPC and RtLPC, respectively]) and bilateral hippocampi (LtHIPP and RtHIPP) (*p* 0.01whole-brain corrected).

Table 1
Sample demographics and clinical variables (*n* 20)

	Contrastedsubjectgroups		Analysis	
	Higher insulin (*n* 10) Mean (SD)	**Lower insulin (*n* 10)**		
Age (y)	59.2 (5.1)	57.1 (4.2)	*t*(18)	1.008, NS
Years of education	15.8 (2.8)	16.1 (1.7)	*t*(18)	0.335, NS
MMSE	28.9 (0.9)	29.5 (1.0)	*t*(18)	1.450, NS
HDRS-17 score	4.7 (2.2)	3.7 (2.1)	*t*(18)	1.046, NS
Age at menopause	45.7 (8.5)	46.8 (7.5)	*t*(18)	0.319, NS
WASI-FSIQ	115.4 (14.8)	126.1 (4.4)	*t*(18) 0.042	2.190, *p*
Executive function (*z*-score)	1.19 (2.61)	1.16 (2.3)	*t*(18) 0.047	2.219, *p*
Verbal memory (*z*-score)	0.86 (5.88)	1.49 (5.03)	*t*(18)	0.259, NS
Visual memory (*z*-score)	0.27 (2.33)	0.51 (1.29)	*t*(18)	0.276, NS
Attention (*z*-score)	0.69 (7.37)	0.97 (3.76)	*t*(18)	0.635, NS
Body mass index	28.4 (2.7)	22.9 (2.1)	*t*(18) 0.01	5.101, *p*
Fasting plasma insulin (IU/mL)	13.2 (6.4)	5.7 (1.9)	*t*(18) 0.01	3.484, *p*
Fasting plasma glucose (mg/dL)	89.7 (12.7)	86.1 (11.2)	*t*(16)	0.673, NS
	% in each group			
History of depression	80	70	^{2} 0.2 67, NS	
APOE -4 allele carrier	40	50	^{2} 0.2 02, NS	
First-degree relative with AD	40	80	^{2} 3.3 33, NS	

Key: AD, Alzheimer's disease; APOE, apolipoprotein E; FSIQ, Full Scale Intelligence Quotient; HDRS, Hamilton Rating Scale for Depression; MMSE, Mini Mental State Examination; NS, not significant; WASI, Wechsler Abbreviated Scale of Intelligence.

Table 2

Functional connectivity results

Brainregion	Brodmannarea	Talairachcoordinates			*t* values	*p* corrected (FDR)	Cluster size(mL)
		X	Y	Z			
Within group: lower insulin group							
Connectivity with DMN seed regions (weighted average of MPFC, PCC, LtLPC, RtLPC)							
Bilateral medial frontal gyrus	10	2	44	7	16.13	0.001	151.0
		6	46	9	15.02		
		18	53	3	14.77		
Left precuneus, bilateral angular gyri	7, 39	7	50	38	15.29	0.001	136.9
		45	65	36	14.31		
		46	66	36	12.92		
Right middle and inferior temporal gyri	21	69	24	12	7.87	0.001	15.6
		69	34	12	6.45		
		63	14	16	6.27		
Left middle and inferior temporal gyri	20, 21	62	23	17	4.96	0.001	10.0
		56	0	24	4.84		
		66	38	11	4.51		
Connectivity with hippocampal seed regions (weighted average of LtHIPP, RtHIPP)							
Bilateral parahippocampal gyri (hippocampus)30		28	18	14	16.51	0.001	134.5
		18	33	6	15.51		
		24	13	14	14.55		
Within group: higher insulin group							
Connectivity with DMN seed regions (weighted average of MPFC, PCC, LtLPC, RtLPC)							
Bilateral anterior cingulate, right medial frontal gyrus		32,	10 44	6	16.04	0.001	144.1
0		18	53	3	14.27		
		8	44	7	12.79		
Bilateral angular gyri, left precuneus	7, 39	45	65	36	15.08	0.001	145.4
		7	50	38	14.97		
		50	64	31	13.26		
Right middle and inferior temporal gyri	21	63	14	16	6.02	0.001	13.8

Brainregion	Brodmannarea	Talairachcoordinates			*t* values	*p* corrected (FDR)	Cluster size(mL)
		X	Y	Z			
		69	24	11	5.16		
		58	18	12	4.88		
Left middle and inferior temporal gyri	20, 21	62	19	17	5.66	0.001	11.7
		56	0	24	5.35		
		58	13	17	5.00		
Left nterior cingulate, bilateral caudate (caudate head)	25	5	1	6	5.16	0.001	10.8
		9	7	2	4.75		
		14	12	1	4.37		
Connectivity with hippocampal seed regions (weighted average of LtHIPP, RtHIPP)							
Bilateral parahippocampal gyri (hippocampus, amygdala)		34	16	13	14.35	0.001	134.5
		29	17	13	13.95		
		27	11	13	13.17		
Left middle temporal gyrus, left fusiform gyrus	21, 22, 37 66		17	3	4.93	0.001	8.7
		60	45	3	4.34		
Between group differences: lower insulin higher insulin Connectivity with MPFC seed regions		45	58	10	4.12		
Left parahippocampal gyrus, thalamus (lateral posterior nucleus)	27	17	39	3	6.51	0.001	12.2
		16	22	13	5.45		
Connectivity with LtHIPP seed regions Right Superior and medial frontal gyri		19	32	1	4.13		
	10	4	61	6	5.96	0.001	12.7
		1	70	8	5.34		
Connectivity with RtHIPP seed regions Right Superior and medial frontal gyri		11	55	6	5.32		
	10, 11	14	59	8	5.61	0.001	11.3
		11	68	5	5.11		
		16	52	1	4.86		

Key: DMN, default mode network; FDR, false discovery rate; HIPP, hippocampus; Lt, left; LPC, lateral parietal cortex; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; Rt, right.