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Region-specific association between basal blood insulin and cerebral glucose metabolism in older adults

Min Soo Byun[a], Hyun Jung Kim[b], Dahyun Yi[a], Hyo Jung Choi[c], Hyewon Baek[d], Jun Ho Lee[e], Young Min Choe[f], Seung Hoon Lee[g], Kang Ko[h], Bo Kyung Sohn[i], Jun-Young Lee[c,j], Younghwa Lee[e], Yu Kyeong Kim[k], Yun-Sang Lee[l], Dong Young Lee[a,e,j,*], for the KBASE Research Group[1]

[a] Institute of Human Behavioral Medicine, Medical Research Center Seoul National University, Seoul, Republic of Korea
[b] Department of Psychiatry, Changsan Convalescent Hospital, Changwon, Republic of Korea
[c] Department of Psychiatry, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea
[d] Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin, Republic of Korea
[e] Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Republic of Korea
[f] Department of Neuropsychiatry, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea
[g] Department of Neuropsychiatry, Bucheon Geriatric Medical Center, Bucheon, Republic of Korea
[h] Department of Neuropsychiatry, National Center for Mental Health, Seoul, Republic of Korea
[i] Department of Psychiatry, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea
[j] Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea
[k] Department of Nuclear Medicine, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea
[l] Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Although previous studies have suggested that insulin plays a role in brain function, it still remains unclear whether or not insulin has a region-specific association with neuronal and synaptic activity in the living human brain. We investigated the regional pattern of association between basal blood insulin and resting-state cerebral glucose metabolism (CMglu), a proxy for neuronal and synaptic activity, in older adults.

Method: A total of 234 nondiabetic, cognitively normal (CN) older adults underwent comprehensive clinical assessment, resting-state 18F-fluodeoxyglucose (FDG)-positron emission tomography (PET) and blood sampling to determine overnight fasting blood insulin and glucose levels, as well as apolipoprotein E (APOE) genotyping.

Results: An exploratory voxel-wise analysis of FDG-PET without a priori hypothesis demonstrated a positive association between basal blood insulin levels and resting-state CMglu in specific cerebral cortices and hippocampus, rather than in non-specific overall cerebral regions, even after controlling for the effects of APOE e4 carrier status, vascular risk factor score, body mass index, fasting blood glucose, and demographic variables. Particularly, a positive association of basal blood insulin with CMglu in the right posterior hippocampus and adjacent parahippocampal region as well as in the right inferior parietal region remained significant after multiple comparison correction. Conversely, no region showed negative association between basal blood insulin and CMglu.

Conclusions: Our finding suggests that basal fasting blood insulin may have association with neuronal and synaptic activity in specific cerebral regions, particularly in the hippocampal/parahippocampal and inferior parietal regions.

1. Introduction

The brain was once considered to be insensitive to insulin, a key hormone that regulates peripheral glucose homeostasis. However, after the presence of insulin and insulin receptors in the brain were reported, several studies have demonstrated the various functions of insulin in

* Corresponding author at: Department of Neuropsychiatry, Seoul National University Hospital, Department of Psychiatry, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
E-mail address: selfpsy@snu.ac.kr (D.Y. Lee).
[1] The list of co-investigators is provided in elsewhere (http://kbase.kr/eng/about/research.php).

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the brain, other than its effect on peripheral glucose regulation via the hypothalamus (Ghasemi et al., 2013; Lee et al., 2016; Mielke and Wang, 2011). Specifically, insulin signaling may play an important role in synaptic plasticity, particularly in hippocampus, and cognitive functions such as learning and memory in the central nervous system (CNS) (Costello et al., 2012; De Felice and Benedict, 2015; Ghasemi et al., 2013; Lee et al., 2016). Previous studies which reported cognitive improvement in cognitively normal (CN) adults after use of intranasal insulin also support the role of insulin in CNS regarding cognitive function (Benedict et al., 2004; Benedict et al., 2007). Moreover, a number of previous studies indicate that deficient insulin signaling may be involved in the pathophysiology of cognitive impairment in older adults as well as neurodegenerative disease such as Alzheimer's disease (AD). First, the effect of intranasal insulin on cognitive tests on patients with cognitive impairments such as mild cognitive impairment (MCI) or AD dementia has been previously reported (Claxton et al., 2015; Craft et al., 2012). Second, both previous preclinical and clinical studies reported that deficient insulin signaling may contribute to AD-related neuropathological changes (i.e., beta-amyloid deposition, tau phosphorylation, and glycogen synthase kinase 3β activity, etc) (Byun et al., 2017a; De Felice and Benedict, 2015; Freiherr et al., 2013; Ghasemi et al., 2013; Jolivalt et al., 2010; Sato and Morishita, 2015; Sims-Robinson et al., 2010; Wang et al., 2010; Yang et al., 2013). In addition, a previous epidemiological study which followed up elderly men over 5 years reported a U-shaped association between the fasting blood insulin levels and risk of AD dementia (Peila et al., 2004), indicating that low fasting blood insulin level as well as hyperinsulinemia indicating peripheral insulin resistance (IR) can also increase the risk of AD dementia. The associations between low fasting basal blood insulin levels and risk of AD dementia have been replicated in a recent study which followed up nondiabetic old-aged women with large sample size for 34 years (Mehlig et al., 2018). These results support insulin's role in neuronal and synaptic functions of the specific brain regions associated with cognition, as well as pathophysiology of AD.

^{18}F-fluodeoxyglucose (FDG)-positron emission tomography (PET) is widely used to measure resting-state cerebral glucose metabolism (CMglu), a proxy for neuronal and synaptic activity and integrity, and to detect regional changes in CMglu in degenerative conditions that affect brain function such as AD or the aging process (Berti et al., 2014; Mosconi, 2013). Because most of the insulin in the brain is primarily transported from peripheral blood via a saturable transport mechanism across the blood-brain barrier (Banks, 2004; Schwartz et al., 1991), investigating the association between blood insulin levels and resting-state regional CMglu measured using FDG-PET can help identify specific brain regions where insulin and its signaling are closely associated with neural function and metabolic status, and will provide more clues for understanding distinct role of insulin in human brain in vivo.

To date, the relationship between blood insulin levels and CMglu assessed using FDG-PET in human brains in vivo has been explored only in a few studies (Bingham et al., 2002; Cranston et al., 1998; Hasselbalch et al., 1999). However, these studies had several limitations, for example, using small sample sizes and evaluating the effects of hyperinsulinemia rather than basal level of fasting blood insulin. Moreover, the regional pattern of the relationship between basal blood insulin levels and in vivo CMglu, particularly in old-aged adults vulnerable to the degenerative process in both the brain (Jack et al., 2014; Mattson and Magnus, 2006) and pancreatic β-cells (Kushner, 2013), has not been investigated. Although a recent study explored the association between fasting blood insulin levels and a neurodegeneration biomarker for AD measured by FDG-PET (Byun et al., 2017a), the previous study used a region-of-interest (ROI) approach which predefined a single ROI that covered only very limited brain regions with a priori hypothesis. Thus, whether basal fasting blood insulin levels are associated with CMglu in other wide regions that were not included in the previous study, and whether it shows a specific pattern of association with selective cerebral regions or nonspecific association throughout the entire cerebrum, remains unknown.

Therefore, we investigated the association between basal fasting insulin levels in blood and regional CMglu in nondiabetic CN older adults with a large sample size, in order to identify whether or not basal fasting blood insulin has a region-specific association with CMglu, an index of neuronal activity and synaptic integrity using a voxel-wise analysis of FDG-PET without a priori hypothesis.

2. Materials and methods

2.1. Recruitment of participants and clinical/neuropsychological assessments

This study was part of an ongoing prospective cohort study, the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), which started in 2014 and aims to identify novel biomarkers for AD and explore various lifetime experiences contributing to AD-related brain changes. The study protocol was approved by the Institutional Review Boards of Seoul National University Hospital and SNU-SMG Boramae Center, Seoul, South Korea, and the study was conducted in accordance with the recommendations of the current version of the Declaration of Helsinki. All subjects provided their written informed consent. Details of the recruitment and methodology used in the KBASE cohort are described elsewhere (Byun et al., 2017a,b).

In brief, all participants underwent standardized KBASE clinical and neuropsychological assessments which incorporated the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) assessment battery (Lee et al., 2004; Lee et al., 2002) by trained psychiatrists and neuropsychologists. The inclusion criteria for CN older adults were as follows: age 55–90 years (inclusive), Clinical Dementia Rating score of 0, and no diagnosis of MCI or dementia. The exclusion criteria were any present serious medical, psychiatric, or neurological disorder that could affect mental functioning; the presence of severe communication problems that would make a clinical examination or brain scan difficult, contraindications for magnetic resonance imaging (MRI) scan; absence of a reliable informant; illiteracy; participation in another clinical trial and treatment with an investigational product.

Comorbid diabetes mellitus (DM) and other vascular risk factors (VRFs) including hypertension, hyperlipidemia, coronary heart disease, stroke, and transient ischemic attack were evaluated through systematic interviews with participants and their informants by trained nurses. Medications were also reviewed based on prescriptions provided by the participants. Regarding other comorbid VRFs, VRF scores (VRSs) were calculated as the number of other VRFs present and are reported as percentages (DeCarli et al., 2004). Height and weight were measured to calculate body mass index (BMI).

As of May 2017, a total of 287 CN older adults were initially recruited. Among them, one participant was excluded from final analysis due to image artifact. Another 47 individuals who were diagnosed with DM in a clinic, taking medication for DM and 5 individuals who had a fasting blood glucose (FBG) level ≥ 126 mg/dL (Korean Diabetes Association, 2015) at the time of examination were excluded from this study at the time of examination having a fasting blood glucose (FBG) level ≥ 126 mg/d, to minimize possibility of including subject with DM and high FBG that might affect FDG-PET scan. Thus, a total of 234 CN older adults were included for the final analysis. A subset of participants (n = 205) was included in the previous study (Byun et al., 2017a).

2.2. Blood laboratory tests

After an overnight fast, blood samples were collected by venipuncture in the morning on the day of [^{18}F]FDG-PET. Fasting serum levels of insulin were measured using a direct chemiluminescent two-site sandwich immunoassay. FBG levels were measured using the

glucose hexokinase method. Genomic DNA was extracted from whole blood and apolipoprotein E (APOE) genotyping was performed as described previously (Wenham et al., 1991). APOE ε4 carrier status was coded if at least one ε4 allele was present.

2.3. PET image acquisition and preprocessing

Participants underwent FDG-PET imaging using a 3.0 T Biograph mMR (PET-MR) scanner (Siemens Healthcare Sector, Erlangen, Germany). The participants fasted for at least 6 h and rested in a waiting room for 40 min prior to scanning after intravenous administration of 0.1 mCi/Kg of [^{18}F]FDG radioligand. Rigid 16 channel head/neck coil was used and small foam earplugs were applied during scan. Radial, tangential and axial spatial resolution of the scanner were 4.2, 4.2, and 4.5 mm full width at half maximum (FWHM) at 1 cm from the field of view (FOV) center, respectively. FDG-PET data were acquired in list mode and reconstructed into 4 frames with a frame length of 5 min by ordered subset expectation maximization algorithm (5 iterations with 21 subsets). The PET data were corrected for attenuation, scatter, random coincidences and radioactive decay. With regard to attenuation correction (AC), AC maps were generated by Biograph mMR software (version VB18P; Siemens) following the manufacturer's instruction, which used segmentation-based AC based on an attenuation map derived from MR images (Schulz et al., 2011). An ultrashort echo time (UTE) sequence was used for MR-based AC. After visually evaluating the data for any significant head movements, the data were reconstructed into a 20-min summed image and images with motion artifacts were excluded from the study. 3D T1-weighted images were acquired in the sagittal orientation using the abovementioned 3.0 T PET-MR machine. MR image acquisition parameters were as follows: repetition time = 1670 ms, echo time = 1.89 ms, FOV 250 mm, and 256 × 256 matrix with 1.0-mm slice thickness.

Image preprocessing was performed using statistical parametric mapping 12 (SPM 12) (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014a (Mathworks, Natick, MA, USA) (Fig. 1). Prior to normalization, approximate manual image re-orientation of each subject FDG-PET image were performed. Using coregister (estimate) function in SPM12, static FDG-PET images were co-registered to individual T1 structural images that were already coregistered to the MNI template.

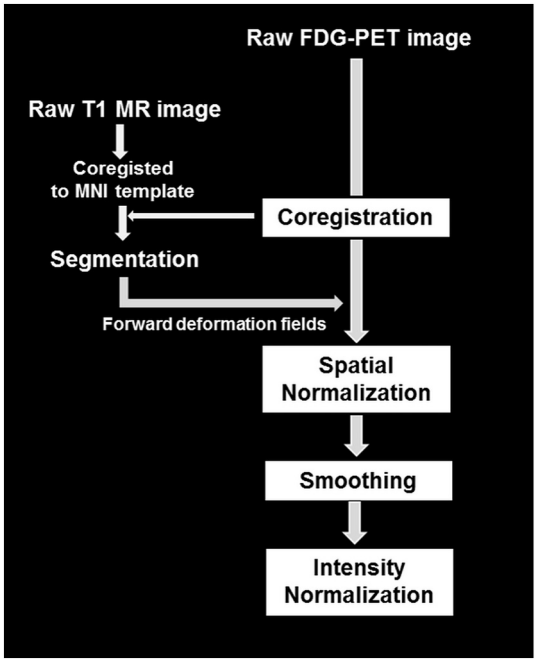

Fig. 1. Flow chart of FDG-PET image pre-processing.

Transformation parameters (i.e., forward deformation fields) were obtained for each subject using the default "Segment" function, which were later applied to the FDG-PET images to spatially normalize to the template space using the normalize (write) function in SPM12. Normalized images were written with isotropic voxel size of 1 mm. All co-registered and spatially normalized images were visually inspected for quality control. Subsequently, spatially normalized images were smoothed with an isotropic Gaussian filter of 12 mm FWMH to increase the signal-to-noise ratio and reduce residual inter-individual variability after spatial normalization (Lange et al., 2016; Pagani et al., 2015; Perani et al., 2014). Finally, intensity normalization was performed using the pons as the reference region (Ewers et al., 2014; Jack et al., 2012; Jagust et al., 2010; Kantarci et al., 2010; Minoshima et al., 1995; Walhovd et al., 2010a; Walhovd et al., 2010b), by applying the pons mask provided by the WFU PickAtlas (http://fmri.wfubmc.edu/software/pickatlas).

2.4. Voxel-wise analyses of FDG-PET image

To investigate cerebral regions showing an association between basal fasting blood insulin level and CMglu, voxel-wise multiple regression analyses were performed with fasting blood insulin level as an independent variable and FDG uptake (standardized uptake value ratio) in each voxel as a dependent variable using the multiple regression model of SPM. To control for possible confounding effects, age, sex, educational level, APOE ε4 carrier status, FBG, VRS and BMI were entered into the multiple regression model as covariates. First, results were initially examined at $p < .001$, $k > 20$ uncorrected for multiple comparisons as an exploratory analysis. Then, significant clusters were identified based on a cluster-correction procedure available in Analysis of Functional NeuroImage (i.e., 3dClustSim, version built Feb 102,017); 10,000 iterations of Monte Carlo simulations were performed on an anatomical cerebral mask dataset with 1,801,748 voxels. This method, derived from Gaussian Random Field Theory, protects against multiple comparisons (Forman et al., 1995). The cluster size threshold to achieve correction for multiple comparisons at $p < .001$ was calculated to be $k > 527$ voxels. Thus, significant clusters after multiple comparison correction were reported at uncorrected $p < .001$ (voxel-level), and $k > 527$ voxels. As this study focused on cerebral glucose metabolic activity, analysis for this study was restricted to the cerebrum and cerebellum was excluded.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are shown in Table 1. A total of 234 nondiabetic CN older adults with an average age of 69.1 (8.3) years old were included in this study. Among those, 123 participants were female (52.6%) and the number of years of education was 11.9 (4.8) years. There were 46 participants with one or more APOE ε4 allele (19.7%). Regarding other cardiovascular risk factors, mean VRS was 16.7 (16.6), average BMI was 24.1 (2.8) kg/m^2, and average FBG and fasting blood insulin levels were 97.7 (9.6) mg/dL and 7.9 (4.4) mIU/L, respectively. Distribution of fasting blood insulin level in participants are described in Supplementary Fig. 1 (Appendix A).

3.2. Voxel-wise analyses of the association between basal blood insulin and CMglu

In an exploratory voxel-wise analysis, fasting blood insulin level showed positive association with several clusters in the bilateral cerebral cortices and right hippocampus (Fig. 2 and Table 2), after controlling for the effects of APOE4 carrier status, VRS, BMI, FBG, and demographic variables (i.e., age, sex, years of education) at uncorrected

Table 1
Demographic and clinical characteristics of participants.

	Participants (N = 234)
Age, years	69.1 (8.3)
Females	123 (52.6%)
Educational level, years	11.90 (4.9)
APOE ε4 carriers	46 (19.7%)
Hypertension	103 (44.0%)
Coronary heart disease	10 (4.3%)
Hyperlipidemia	80 (34.2%)
Stroke	0 (0%)
TIA	2 (0.9%)
VRS	16.7 (16.6)
BMI (kg/m^2)	24.1 (2.8)
SBP (mmHg)	124.5 (16.4)
DBP (mmHg)	76.6 (10.9)
Fasting blood glucose (mg/dL)	97.7 (9.6)
Fasting blood insulin (mIU/L)	7.9 (4.4)

NOTE. Data are presented as mean (SD) or n (%).
Abbreviation: APOE, Apolipoprotein E; DM, Diabetes mellitus; TIA, Transient ischemic attack; VRS, Vascular risk factor score; BMI, Body mass index; SBP, Systolic blood pressure, DBP, Diastolic blood pressure.

p < .001, k > 20. First, the largest cluster was observed in the right posterior hippocampus and adjacent parahippocampal region, which extends to the part of retrosplenial cortex (Cluster 1). Second, CMglu in the right inferior parietal region, mainly in the right angular gyrus, showed positive association with fasting blood insulin levels (Cluster 2). In addition, our exploratory voxel-wise analysis found more clusters that showed positive associations between fasting blood insulin levels and CMglu in the left inferior parietal region including the left supramarginal gyrus (Cluster 3), and left parahippocampal and fusiform gyrus (Cluster 4), as well as in the right subcallosal area (Cluster 5) and left uncus (Cluster 6). Conversely, no regions showed negative associations between basal blood insulin levels and CMglu even at the exploratory analysis level.

After multiple comparison correction using cluster-extent based thresholding (uncorrected p < .001, k > 527), positive associations between CMglu and basal blood insulin levels in the right posterior hippocampal/ parahippocampal region (Cluster 1; Fig. 3A) and right inferior parietal regions, mainly in the right angular gyrus (Cluster 2; Fig. 3B) remained significant.

4. Discussion

Our voxel-wise analysis without a priori hypothesis revealed that basal fasting blood insulin levels were associated with resting-state CMglu in specific cerebral regions including the right posterior hippocampal/parahippocampal and inferior parietal regions, suggesting a region-specific pattern of association between fasting blood insulin levels and CMglu in nondiabetic CN older adults. In addition, only a positive association between basal fasting blood insulin levels and regional CMglu was observed, whereas no regions showed an inverse correlation with fasting blood insulin levels, even after controlling for possible confounding factors that can affect blood insulin levels or CMglu such as VRS, BMI, FBG, APOE4 carrier status and demographic variables including age, sex and educational level.

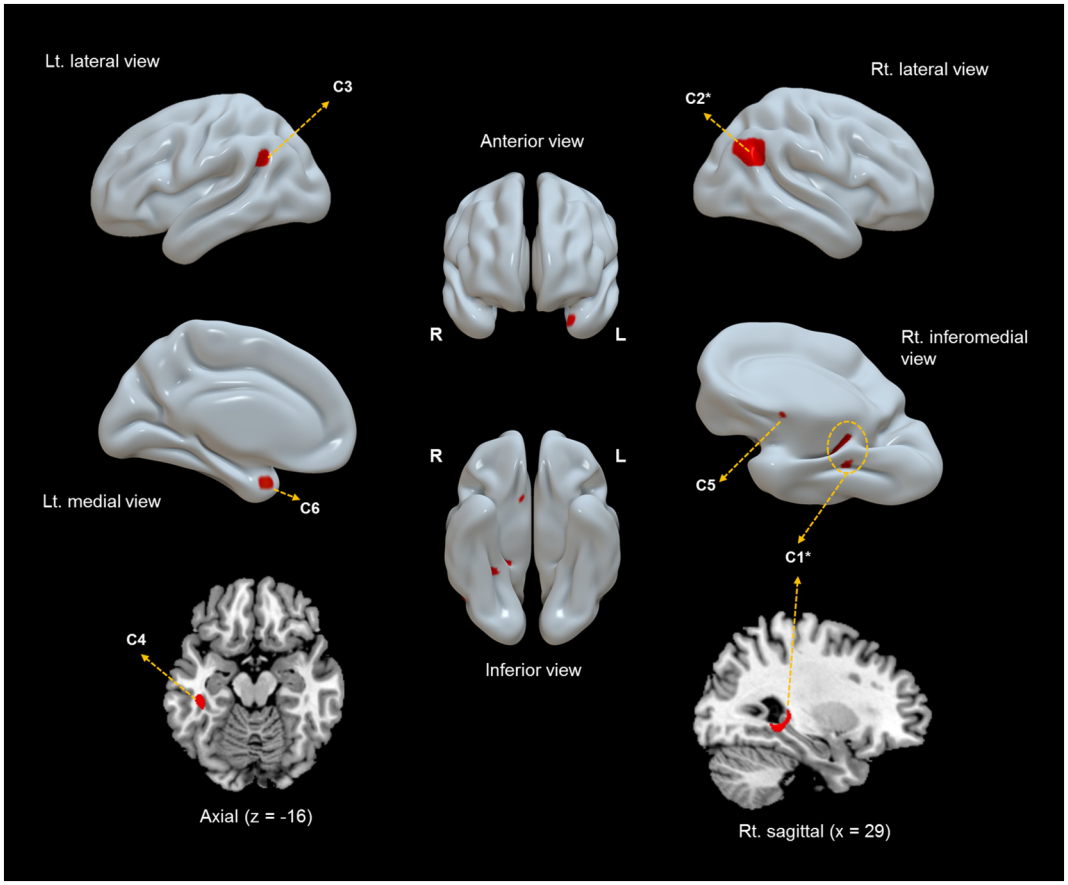

Fig. 2. The result of an exploratory voxel-wise analysis that identified regions shown positive association between fasting basal blood insulin levels and resting-state CMglu measured by ^{18}F-FDG-PET are demonstrated after adjusting age, sex, education, APOE ε4 carrier status, FBG, VRS and BMI (uncorrected p < .001, k > 20) are showed. Number of clusters (e.g. C1) corresponds to those in Table 2. *Significant after multiple comparison correction using cluster-correction procedure (uncorrected p < .001, k > 527). Abbreviation: CMglu, cerebral glucose metabolism, FDG-PET, fluorodeoxyglucose-positron emission tomography, APOE, apolipoprotein E

Table 2
Neuroanatomical regions and MNI coordinates of local maxima of clusters shown positive associations between basal fasting blood insulin level and CMglu in an exploratory voxel-wise analysis (uncorrected p < .001, k > 20).

No.	Neuroanatomical region	Cluster size (voxels)	Peak					
			Local maxima	MNI coordinates			T-value	P-value[a]
				x	y	z		
C1*	Posterior part of hippocampus and adjacent parahippocampal region, a part of retrosplenial region (R)	1356	Posterior hippocampus (R)	29	−40	−2	3.62	0.00018
C2*	Inferior parietal region (R)	1224	Angular gyrus (R)	49	−60	31	3.53	0.00025
C3	Inferior parietal region (L)	442	Angular gyrus (L)	−48	−50	30	3.55	0.00023
C4	Parahippocampal and fusiform gyrus (L)	392	Fusiform gyrus (L)	−42	−30	−16	3.38	0.00043
C5	Subcallosal area (R)	124	Subcallosal gyrus (R)	5	9	−21	3.33	0.00051
C6	Uncus (L)	71	Uncus (L)	−27	7	−31	3.21	0.00075

NOTE. Number of clusters are labeled for each cluster (i.e. C1 denotes cluster no.1).
* Significant after multiple comparison correction using cluster-correction procedure (uncorrected p < .001, k > 527).
[a] Uncorrected p-value of peak voxel.

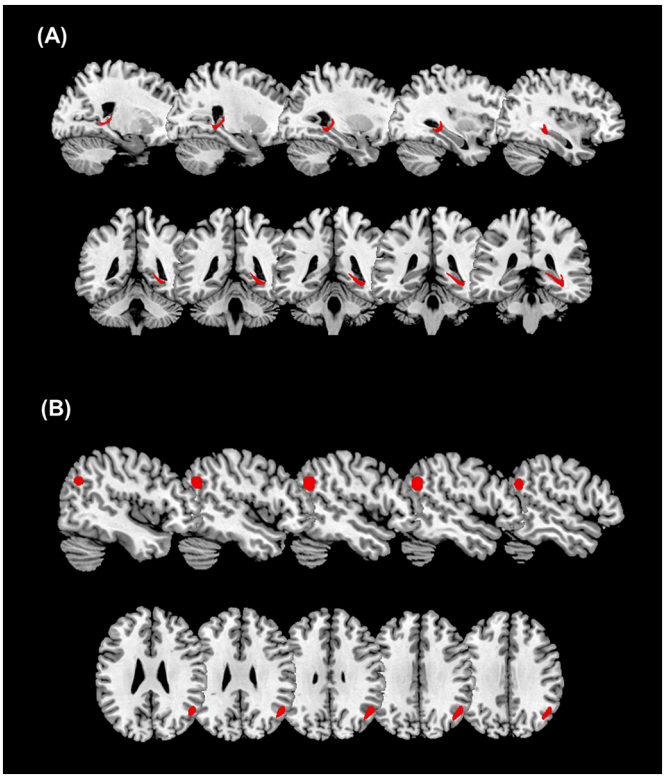

Fig. 3. The axial, sagittal and coronal images demonstrating significant clusters after multiple comparison correction using a cluster-correction procedure (uncorrected $p < .001$, $k > 527$): (A) sagittal (upper) and coronal (lower) images showing Cluster 1 in the right posterior hippocampus, adjacent parahippocampal region, and part of retrosplenial region, (B) sagittal (upper) and axial (lower) images showing Cluster 2 in the right angular gyrus.

The present study measured basal blood insulin levels in the physiologic range of the fasting state and investigated whether regional CMglu varies according to the basal fasting blood insulin level within physiologic range, which is major distinction between the current and previous studies reporting negative results (Cranston et al., 1998; Hasselbalch et al., 1999). These previous studies used experimental techniques such as hyperinsulinemic-euglycemic clamps to artificially induce acute hyperinsulinemia that is beyond the physiological range of fasting blood insulin. Average plasma insulin levels in hyperinsulinemic condition in these previous studies (Cranston et al., 1998; Hasselbalch et al., 1999) were over 70–191 mIU/L during eugycemic clamping, which were much higher than upper normal limit of fasting blood insulin level in physiologic range previously reported (i.e., ≤30 mIU/L) (DiNicolantonio et al., 2017). In addition, different sample characteristics (i.e. young or middle-aged, comorbid DM) and small sample size in those previous studies (Cranston et al., 1998; Hasselbalch et al., 1999) makes it difficult to directly compare the results of previous studies to ours. In a previous study (Cranston et al., 1998), all 10 participants were male who had insulin-dependent DM in their 40s, with > 20 years of disease duration. In another previous study (Hasselbalch et al., 1999), age range of all 16 participants was 21 to 35 years. Thus, such differences in experimental conditions and participants' demographic and clinical characteristics should be considered when interpreting negative findings on the association between increase of peripheral blood insulin level and glucose metabolic rate in these two previous studies (Cranston et al., 1998; Hasselbalch et al., 1999). In contrast, one previous study reported a positive association between increased blood insulin levels and global cerebral glucose uptake in nondiabetic middle-aged males (Bingham et al., 2002). Although sample size of this previous study was small ($n = 8$), and exogenous insulin and somatostatin was intravenously infused to participants for experimental conditions, blood insulin levels in that previous study were close to the upper limit of the physiological range of fasting insulin. Taken into consideration of these previous findings, our results indicate that basal blood insulin levels in the physiologic range of the fasting state, rather than hyperinsulinemic conditions such as the postprandial state, might be positively correlated with regional CMglu in selective cerebral regions, at least in nondiabetic older adults.

We found the significant clusters with positive association between basal fasting blood insulin levels and resting-state CMglu in the right posterior hippocampal/parahippocampal region, as well as in the right inferior parietal region, particularly in the right angular gyrus, after multiple comparison correction. A previous study (Byun et al., 2017a) reported the association between blood insulin level and CMglu of a single composite ROI which consisted of the bilateral angular gyri, inferior temporal and posterior cingulate cortices (Jack et al., 2014). Based on our findings, it can be inferred that the association between blood insulin levels and CMglu in the angular gyrus might substantially contribute to the result of a previous study (Byun et al., 2017a). Moreover, by adopting voxel-wise analysis without a priori hypothesis, this study could detect other significant cluster in the right posterior hippocampus and adjacent hippocampal region - which was not captured by an ROI-based approach focusing on a single predefined ROI (Byun et al., 2017a). In addition, our exploratory voxel-wise analysis (uncorrected $p < .001$, $k > 20$) detected more clusters in the left parahippocampal/fusiform gyrus, left inferior parietal region including the angular gyrus, as well as in the right subcallosal area and left uncus, although these clusters did not remain significant after multiple comparison correction using cluster-extent based thresholding (i.e.,

uncorrected p < .001, k > 527). When a more lenient *p*-value was used for initial examination with re-calculated cluster-extent based threshold (uncorrected *p* < .005, k > 1062), positive associations between fasting blood insulin levels and CMglu were similarly observed in the abovementioned regions including the bilateral hippocampal/parahippocampal and inferior parietal regions (Appendix A; Supplemental Fig. 2 and Supplemental Table 1). Thus, although we found significant clusters in the right posterior hippocampal/parahippocampal and inferior parietal regions, findings from our exploratory voxel-wise analysis might provide clues that similar, but relatively weaker relationships between fasting blood insulin levels and CMglu may exist in the similar regions in the left hemisphere, which needs to be further validated.

The largest cluster shown significant association between fasting blood insulin levels and CMglu was in the posterior part of hippocampus and adjacent parahippocampal region of the right hemisphere. These structures are well-known for their key roles regarding various cognitive functions such as learning, memory, object recognition and processing (Baumann and Mattingley, 2016; Dou et al., 2005; Duzel et al., 2003; Fanselow and Dong, 2010; Lee et al., 2017; Strange et al., 1999; Thangavel et al., 2008; Zhao et al., 1999). Our findings are in accordance with previous literatures reporting insulin's effects on cognitive improvement and a link between deficient neuronal insulin signaling and hippocampal synaptic plasticity in animal models or humans (Costello et al., 2012; Dou et al., 2005; Ghasemi et al., 2013; Lee et al., 2016; Zhao et al., 1999), as well as a previous functional MRI study in which insulin reportedly affected the neuronal response in the medial temporal lobe in humans (Rotte et al., 2005). In addition, this cluster seems to extend towards the part of right retrosplenial region (BA 30), where reciprocal connections between hippocampal formation, parahippocampal region, and parietal cortex exists (Vann et al., 2009). Of note, only the posterior, but not the anterior part of hippocampus and parahippocampal gyrus showed significant association with basal blood insulin levels in this study. According to a number of previous studies that reported differences in functions and genetic expressions between the posterior and anterior hippocampus (Fanselow and Dong, 2010; Lee et al., 2017; Strange et al., 1999), the posterior hippocampus is primarily involved in memory and spatial navigation, while the anterior hippocampus is related to stress and emotion. The posterior parahippocampal gyrus is also known for its function regarding memory processing and its association with AD pathologies such as neurofibrillary tangles (Thangavel et al., 2008). Interestingly, the relationship between posterior part of hippocampus/parahippocampa gyrus and aging process have been reported: A functional connectivity of posterior hippocampus was reported to become more dominant in old-aged adults compared to young adults (Blum et al., 2014), and posterior part of parahippocampal gyrus was selectively vulnerable to age-related memory decline compared to middle or anterior part of parahippocampal gyrus (Burgmans et al., 2011). Thus, considering that participants of our study was old-aged adults, the link between basal blood insulin levels and CMglu in these structures might be partially related to preferential vulnerability of these key structures for cognition to aging process.

We also found a significant association between basal blood insulin level and the resting state CMglu in the right inferior parietal region, mainly in the angular gyrus. The angular gyrus is a part of the heteromodal parietal association cortex (Seghier, 2013), which is a higher-order cortical field involved in various functions including spatial attention, sensory processing and sensorimotor integration (Igelstrom and Graziano, 2017; Seghier, 2013; Singh-Curry and Husain, 2009). It is also major network hub of the various network in human brain (i.e., default mode network, frontoparietal control network, ventral attention network, etc.), and its close relationship with extensive training induced brain plasticity in adults have been previously reported (Igelstrom and Graziano, 2017; Seghier, 2013). Like the hippocampus and parahippocampal gyrus, the inferior parietal regions is also concerned to be vulnerable to neurodegeneration from the early stage of AD (Jacobs et al., 2012).

A possible molecular mechanism regarding insulin's role in these cerebral regions can be inferred based on common characteristics of these specific regions - hippomcapal/parahippocampal regions and inferior parietal cortices – that showed positive associations with basal fasting blood insulin levels. First, considering the glucoregulatory function of insulin through glucose transporters and the expression of the insulin-sensitive glucose transporter GLUT-4 in the hippocampus (Choeiri et al., 2002; McCall et al., 1997; Schulingkamp et al., 2000), a positive association between insulin levels and CMglu in certain regions is hypothetically mediated by an insulin-sensitive glucose transporter such as GLUT-4. However, because most of the glucose transporters located in the central nervous system (CNS) are insulin-insensitive (i.e., GLUT-1 and GLUT-3), and GLUT-4 is located in the only restricted area with very low density (Schulingkamp et al., 2000; Shah et al., 2012), other mechanisms not mediated by the direct action of insulin on glucose transporters also needed to be considered. In this context, effects of insulin on neuronal/synaptic activity and integrity via insulin binding with insulin receptors (Chiu et al., 2008; Mielke and Wang, 2011; Tanaka et al., 1995; Zhao et al., 2004) might be involved in a region-specific association between basal blood insulin and CMglu observed in our study. The brain regions where fasting blood insulin was associated with CMglu in our study correspond with the regions enriched with insulin bindings in animal models and postmortem human brains, such as limbic structures (i.e., hippocampus), and neocortices including parietal cortices (Havrankova et al., 1978; Hill et al., 1986; Marks et al., 1990). Moreover, insulin receptors are reported to be abundant in regions that contain dendritic fields receiving rich afferent synaptic inputs (Frolich et al., 1998; Werther et al., 1987), such as higher-order association cortices and hippocampal structures as observed in our study, suggesting that these regions might have specific association with fasting blood insulin via insulin receptor-related mechanism. Particularly, older adults are more prone to age-related changes in both brain and pancreas, as chances to be exposed to age-related neurodegeneration or neurodegenerative disease (Jack et al., 2014; Mattson and Magnus, 2006), as well as age-associated deterioration of pancreatic β-cell function (Kushner, 2013) are increasing compared to younger adults. Thus, demographic characteristics of our sample (i.e., older adults) needs to be considered when interpreting the current finding, and further studies will be necessary to explore whether positive association between fasting blood insulin and CMglu with region-specific manner is observed in individuals with different age range.

We found no regions that showed negative association between basal fasting blood insulin and resting state CMglu. A previous study that investigated the effect of peripheral IR on CMglu using FDG-PET reported negative association between IR index (i.e., HOMA-IR) and regional CMglu (Baker et al., 2011). However, this finding was only observed in diabetic and prediabetic patients, not in healthy controls. Above all, an IR index such as HOMA-IR is different from blood insulin level itself, as FBG levels multiplies to fasting blood insulin levels when calculating HOMA-IR (Baker et al., 2011). Moreover, a range of blood insulin levels and definition of hyperinsulinemia should be considered when comparing our results with a previous study reporting the association between hyperinsulinemia and risk of dementia (Luchsinger et al., 2004). This previous study defined hyperinsulinemia as fasting blood insulin > 27 mIU/L (Luchsinger et al., 2004). However, according to other previous large-scale epidemiological study that followed up elderly men for 5 years (Peila et al., 2004), both high (> 23 mIU/L) and low (< 7.2 mIU/L) levels of fasting blood insulin levels were associated with increased risk for AD dementia, proposing a "U-shaped" association between fasting blood insulin level and risk of AD dementia. Furthermore, a recent study which followed up non-diabetic women for 34 years reported nonlinear associations between the low fasting blood insulin levels at baseline and increased risk of AD dementia (Mehlig et al., 2018). When we applied cut-off values to

define high fasting blood insulin levels in previous studies – 23 mIU/L (Luchsinger et al., 2004) and 14.8 mIU/L (Mehlig et al., 2018), most of our participants had their fasting blood insulin level under these cut-offs (< 23mIU/L; 99%, and < 14.8mIU/L; 93.6%). Thus, our findings on positive associations between fasting blood insulin levels and regional CMglu in nondiabetic CN older adults might be related to fasting blood insulin's action when it is lower than cut-off threshold for U-shaped or nonlinear association (i.e. within physiological range of fasting blood insulin).

Our study has several strengths. First, data obtained from well-characterized nondiabetic CN older adults with a relatively large sample size were used for the analysis. Second, to minimize possible confounding effect, various covariates that might confound results were all considered. In addition, our study contributes to elucidating the relationship between physiologic range of basal fasting blood insulin levels and resting-state CMglu in the selective cerebral regions.

Nevertheless, there are several limitations in the present study. Because we measured CMglu only at resting state and measured blood insulin levels in fasting condition, particularly in nondiabetic CN older adults group, it is still uncertain whether such regional patterns of association between blood insulin and CMglu will be observed in different conditions (i.e., task-activated state, postprandial conditions or hyperinsulinemia over physiologic range) or populations with different characteristics (i.e., comorbid DM or cognitive impairment such as dementia). In addition, as our study was cross-sectional in design, future longitudinal follow-up studies are necessary to determine the causal relationship between basal fasting blood insulin levels and alterations of CMglu. Further studies on the relationship between CMglu in specific cerebral regions associated with fasting blood insulin levels and behavioral data such as neuropsychological test score, and more intensive research to build up comprehensive model to explaining the CMglu with fasting blood insulin level will be necessary. Furthermore, future studies using more specific imaging ligands to visualize direct binding of insulin with insulin receptors in vivo human brain will be needed to validate hypotheses suggested by this study.

5. Conclusion

In conclusion, we identified a region-specific association between basal fasting blood insulin levels and resting-state CMglu in nondiabetic CN older adults. Our finding suggests that basal fasting blood insulin in physiologic range might have association with neuronal and synaptic activity in specific cerebral regions, particularly in the hippocampal/parahippocampal and inferior parietal regions. Further studies to elucidate underlying mechanism of a region-specific association of fasting blood insulin levels with CMglu in these regions will be necessary.

Conflict of interest and source of funding

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Appendix A. Supplementary data

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