# Insulin Resistance and Cognitive Impairment: Evidence From Neuroimaging

Ying Cui, PhD,[1] Tian-Yu Tang, PhD,[2] Chun-Qiang Lu, PhD,[1] and Shenghong Ju, PhD[1]*

Insulin is a peptide well known for its role in regulating glucose metabolism in peripheral tissues. Emerging evidence from human and animal studies indicate the multifactorial role of insulin in the brain, such as neuronal and glial metabolism, glucose regulation, and cognitive processes. Insulin resistance (IR), defined as reduced sensitivity to the action of insulin, has been consistently proposed as an important risk factor for developing neurodegeneration and cognitive impairment. Although the exact mechanism of IR-related cognitive impairment still awaits further elucidation, neuroimaging offers a versatile set of novel contrasts to reveal the subtle cerebral abnormalities in IR. These imaging contrasts, including but not limited to brain volume, white matter (WM) microstructure, neural function and brain metabolism, are expected to unravel the nature of the link between IR, cognitive decline, and brain abnormalities, and their changes over time. This review summarizes the current neuroimaging studies with multiparametric techniques, focusing on the cerebral abnormalities related to IR and therapeutic effects of IR-targeting treatments. According to the results, brain regions associated with IR pathophysiology include the medial temporal lobe, hippocampus, prefrontal lobe, cingulate cortex, precuneus, occipital lobe, and the WM tracts across the globe. Of these, alterations in the temporal lobe are highly reproducible across different imaging modalities. These structures have been known to be vulnerable to Alzheimer's disease (AD) pathology and are critical in cognitive processes such as memory and executive functioning. Comparing to asymptomatic subjects, results are more mixed in patients with metabolic disorders such as type 2 diabetes and obesity, which might be attributed to a multifactorial mechanism. Taken together, neuroimaging, especially MRI, is beneficial to reveal early abnormalities in cerebral structure and function in insulin-resistant brain, providing important evidence to unravel the underlying neuronal substrate that reflects the cognitive decline in IR.
**Evidence Level:** 5
**Technical Efficacy:** Stage 2

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With the increasing aging population, the prevalence of dementia is expected to be ever increasing globally. The World Health Organization reported that more than 55 million people live with dementia in 2021, and the number is expected to rise to 139 million in 2050.[1] Alzheimer's disease (AD) is the leading cause of dementia, contributing to 60%–70% of all cases. Other major forms include vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Currently, the treatments for dementia are mostly symptom targeted, showing quite limited clinical benefits.[2] Given that dementia is associated with high incidence of disability and dependence, as well as significant social and economic impact, it is of great value to identify modifiable factors to delay or prevent the development of dementia.

Insulin is an endocrine peptide best known for modulating glucose homeostasis. Apart from its peripheral effects, it has been increasing recognized to play a multifaceted role in the brain physiology including neuronal development, glucose regulation, feeding behavior, and cognitive processes such as attention, executive functioning, learning, and memory.[3] Decreased sensitivity to insulin action is the major feature of type 2 diabetes (T2DM) and several other metabolic disorders such as glucose intolerance, obesity and dyslipidemia, which are suggested to be related to impairments in cognitive functioning.[4] Due to the vital role of insulin in brain physiology, IR has been consistently proposed as an important risk factor for developing neurodegeneration and AD neuropathology.[5]

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*Address reprint requests to: S.J., Department of Radiology, Zhongda Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao Road, Nanjing 210009, China. E-mail: jsh0836@hotmail.com

From the [1]Department of Radiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China; and [2]Jiangsu Key Laboratory of Molecular and Functional Imaging, Department of Radiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

 

Epidemiological studies have long been indicated the association between AD and impaired insulin sensitivity, even without the presence of concurrent T2DM and systemic IR.[6] In a Rotterdam study, a doubling of basal insulin levels was associated with a 40% increased likelihood of converting to AD at a 3-year follow-up from baseline, the results remained after removal of T2DM patients.[7] Reduced insulin receptors and receptor affinity were found in AD patients compared with controls.[8] Conversely, AD patients are also more likely to develop disturbed glycemic control, with as high as 80% to be diagnosed as either T2DM or impaired fasting glucose level.[9] These results prompted some investigators to refer AD as "type 3 diabetes" or "insulin-resistant brain state."[8] The close link between IR and AD could be further supported by the beneficial outcome of insulin administration on cognitive functioning.[10] Pathologically, it has been hypothesized that IR promotes the aggregation of Aβ proteins and tau phosphorylation, which further interrupts insulin functioning and exacerbate AD pathology.[11] Other hypotheses include IR-induced impairments in hippocampal plasticity, brain inflammatory reaction, and increased ApoE ε4 allele involvement.[12] The exact mechanism of IR-related cognitive impairment still awaits further research, which will facilitate the development of targeted prevention and treatment strategies.

Neuroimaging has provided an effective in vivo approach to investigate the cerebral changes in the context of neurodegeneration. Among various imaging techniques, MRI has been mostly applied due to its highest brain tissue resolution and versatile contrasts to evaluate structural and functional measurements. Conventional MRI contrasts such as T1WI, T2WI, and FLAIR are commonly used to detect macrostructural changes, which usually occur in a later stage of cognitive impairment. In comparison more advanced and sensitive techniques such as functional, diffusion and perfusion MRI have been increasingly utilized to identify imaging biomarkers that precede clinical manifestations of dementia, which may indeed lead to early detection and halting of disease progression.[13] Other imaging techniques such as Positron Emission Tomography (PET) and ultrasound could also provide additional metabolism and hemodynamic measurements.

The present review aims to summarize recent neuroimaging studies and provides an overview of various brain alterations associated with IR and its related cognitive decrements. The beneficial effects of IR-targeted interventions on brain imaging measurement will also be addressed. These results are expected to provide evidence for the neural substrates of cognitive impairment in patients with reduced insulin sensitivity, as well as to guide future research to apply more appropriate imaging approach and develop effective therapeutic treatments. Given that IR is not a specific disease, but the common feature of a list of metabolic disorders such as aging, diabetes, dyslipidemia, and hypertension, the included neuroimaging studies were on either asymptomatic subjects or various metabolic disorders. Imaging techniques, results demonstrating IR-related brain abnormalities, and their relevance to cognitive impairment will be displayed and discussed.

## The Role of Insulin in Central Nervous System

Insulin has long been recognized as the regulator of peripheral glucose homeostasis, by promoting glucose uptake and inhibiting glucose production.[14] In the past decades, the multifaceted role of insulin in the central nervous system (CNS) has gained more attention. Secreted by pancreatic beta cells, insulin enters the CNS by crossing the blood–brain barrier (BBB) through a receptor-mediated mechanism,[15] although there is still debate as to whether insulin can be synthesized de novo in CNS. Insulin receptors and components of the insulin signaling pathway are widely distributed in the brain, especially in cognition-related regions, such as cerebral cortex, olfactory bulb, hippocampus, and hypothalamus.[16] Given its high affinity in limbic and cognitive regions, it is expected that insulin not only affects brain metabolism through glucose regulation but also has a crucial role in the maintenance of cognitive functioning.[4,10] Furthermore, considerable studies have documented the effect of insulin on excitatory synapses development and dendritic spine formation.[17] Therefore, insulin is vital for brain health and its dysregulation could contribute to multifaceted impairments in cerebral physiology and cognitive activities. The physiological effects of peripheral and central insulin and their coordination are summarized in Fig. 1.

## Insulin Resistance in the Brain

Insulin resistance (IR) refers to reduced sensitivity of target tissues to physiological concentrations of insulin, leading to hyperinsulinemia and glucose dysregulation. Although peripheral IR has long been recognized as the core feature of T2DM, poor insulin sensitivity is also a common characteristic of metabolic disorders such as glucose intolerance, obesity, and hyperlipidemia.[4] A number of genetic and environmental factors such as aging, lack of exercise, smoking, and stress could contribute to the development of IR.[18] While long-term hyperinsulinemia has multiple effects, the most well-known one is the presence of hyperglycemia, leading to adverse effects on brain function via the accumulation of advanced glycation end products, oxidative stress, and glucose neurotoxicity.[19] Furthermore, hyperinsulinemia itself could also damage the brain through downregulating BBB insulin receptors and decreasing the insulin transported into the brain.[6] Until now, whether IR in the periphery and CNS can exist independently is not clear yet, but the relationship between central and peripheral function of insulin is often reciprocal[10] (Fig. 1). Taken together, the effects of long-term

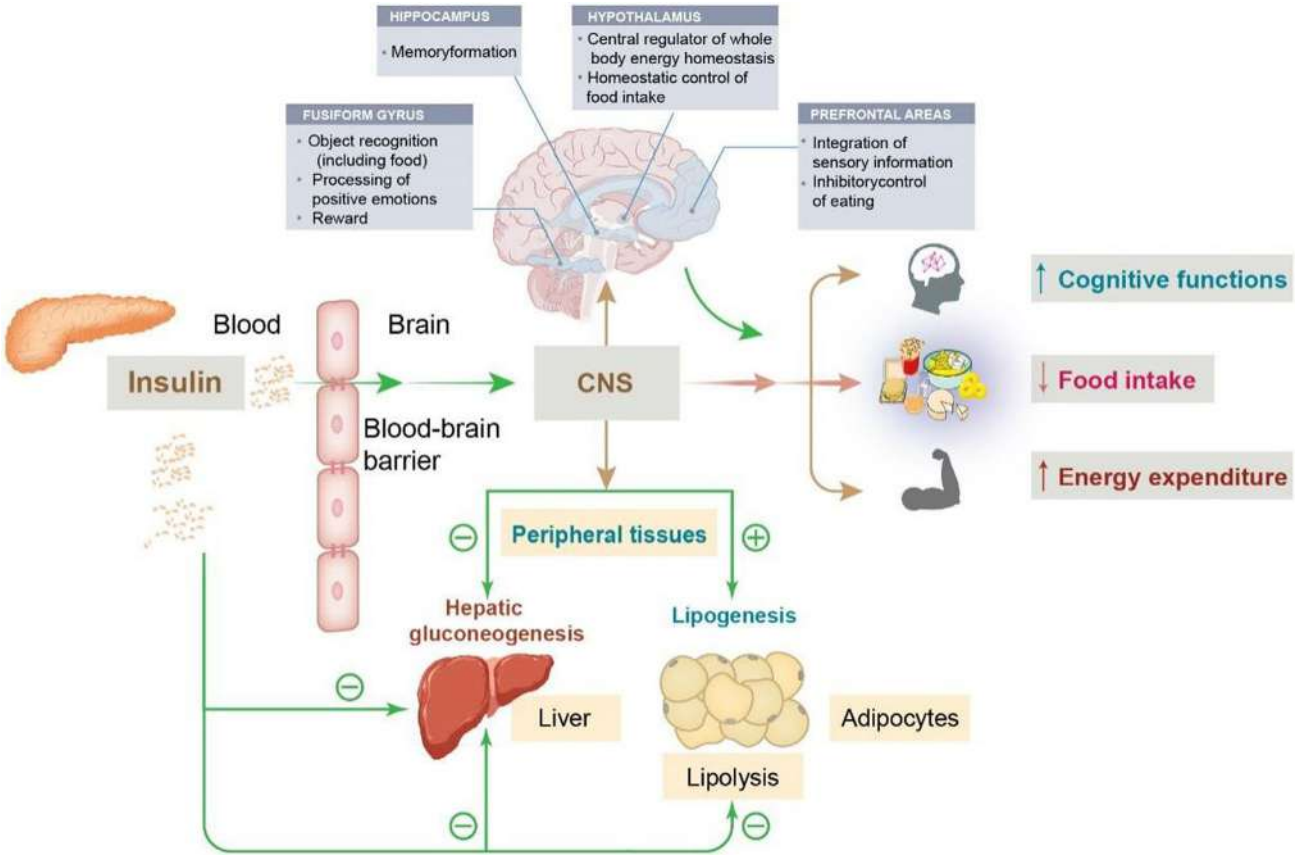


**FIGURE 1: Schematic model of the physiological effects of central nervous and peripheral insulin. Secreted from the pancreas, insulin crosses the BBB via a receptor-mediated process. These receptors are distributed widely in the brain, especially in prefrontal cortex, hippocampus, lingual gyrus, and hypothalamus. By acting on these relevant brain structures, insulin functions to improve cognition, reduce food intake after meal, and promote energy expenditure. Meanwhile, central nervous insulin also facilities peripheral insulin to inhibit hepatic gluconeogenesis and regulates adipocyte metabolism. BBB = blood–brain barrier.**

dysregulation of insulin could go beyond diabetes development, resulting in further impairments in brain metabolism and neuronal activity.

## Metabolic Syndrome and Cognitive Impairment

Given its central role of brain health maintenance, insulin has long been implicated in the development of cognitive impairment and dementia. As the well-known disease characterized of IR, the close link between T2DM and cognitive impairment has been consistently reported.[20] Epidemiologic evidence demonstrated that the risk of developing dementia is 1.5–2 times higher in T2DM patients compared with their healthy cohorts, with insulin-treated patients (i.e., higher disease severity) at the highest risk.[21] According to large-scale clinical studies, the type of T2DM-associated dementia includes not only vascular dementia but also AD. As stated in one study on Japanese-Hawaiian cohorts, diabetes patients showed a 1.5-, 1.8-, and 2.3-fold increased risk of total dementia, AD, and VD, respectively.[22] However, there is little pathological evidence that directly link T2DM with AD, although the CSF tau concentration and neocortical tau deposition are increased in diabetic subjects comparing to healthy controls.[23] Given that both hyperglycemia and insulin could directly affect brain metabolism and function, whether the cerebral complications of T2DM are consequences of brain insulin dysfunction or are due to co-occur diabetic comorbidities are yet to be elucidated.

Meanwhile, patients with other metabolic disorders are also reported to perform worse in cognitive tests. As a major consequence of IR, dyslipidemia is often caused by disturbed insulin signaling in lipolysis and lipogenesis. Since the brain contains the highest level of cholesterol in the body (approximately 20% of whole-body cholesterol),[24] perturbations in lipid metabolism could have a profound effect on brain functioning. A 30-year longitudinal study demonstrated that subjects with central obesity show doubled risk of dementia, independent of age, sex, diabetes, hypertension, and several other cardiovascular risk factors.[25] Another meta-analysis comprising 18 studies showed consistent association between high midlife total cholesterol and an increased risk of dementia.[26] However, there are indeed studies with mixed results, showing no relation or even protective role of cholesterol for cognition.[27]

Taken together, the relationship between IR and cognitive impairment in the background of metabolic disorders is more complicated, which might be driven by multiple factors and still need further clarification.

## Evidence From Neuroimaging

Neuroimaging provides an effective way to in vivo characterize the cerebral abnormalities in various brain disorders. The imaging parameters vary from brain structure to function, providing both localized and quantified biomarkers for exploration of the underlying mechanism. Such neuroimaging studies could thus guide future research into the exploration of clinical correlation, risk factors and prevention strategy. To overview the published articles, we searched "insulin resistance" and ("neuroimaging" OR "brain imaging") in Web of Science up to December 2021 and confined the results to "human studies" and "language in English," excluding review literature. After a careful review of the 494 entries, 178 articles were kept that were directly related to IR and neuroimaging. The published year and keywords distribution map are shown in Fig. 2. Since a considerable number of these articles only presented imaging differences between patients with and without metabolic disorders, instead of the correlation between imaging parameters and IR, most of them will not be described in details in this review.

In the following sections, neuroimaging results focusing on the relation between IR and brain abnormalities will be present, which will include but not limit to cerebral volume, small vessel disease, perfusion, neural function, and metabolism. MRI will be concentrated due to its wide application, versatile parameters, and sensitivity. Meanwhile, as promising therapeutic approaches for dementia, the cerebral effects of IR-targeting treatments will also be discussed. These techniques and results will be summarized to reveal brain abnormalities in IR and are expected to elucidate the nature of the link between IR, cognitive decline, and brain abnormalities. An overview of the main imaging techniques included is shown in Fig. 3, while the main results are displayed in Table 1.

## Brain Atrophy

### *Methodological Review*

Brain atrophy is defined as the shrinkage of brain tissue, resulting from the loss of neurons and neuronal interconnections.[96] MRI, with high soft tissue resolution and versatile measurements, is the most widely applied imaging technique and also remains the only clinically recommended modality in the evaluation of dementia.[97] Brain atrophy is typically assessed using either conventional T1WI sequence for visual inspection, or a high-resolution 3D T1WI sequence, usually the magnetization-prepared rapid gradient-echo (MP-RAGE), at an isotropic resolution of at least 1 mm for research purpose.[98] In clinical settings, assessment of brain volume mainly relies on visual ratings of remarkable atrophy and search of anatomical variations but usually leads to inadequate interobserver reproducibility, and insensitivity in evaluating early cognitive impairment.[99] Therefore, developing quantitative analyses on high-resolution T1 images are necessary to better depict the volumetric changes, especially in research settings.

Recent advances in computer-based methodology for analyzing structural information have led to significant progress in neuroimaging studies. A classical method is the regions of interest (ROIs) approach using manual tracing, which depends on anatomical knowledge and strong prior hypothesis. However, it is often time-consuming, resulting in intraobserver and interobserver bias and limited results confined to the selected ROIs. More advanced methods based on automatic analyses have thus been developed, among which the voxel-based morphometry (VBM) is the most frequently applied thus far.[100] It allows voxel-based analyses by warping MR images into stereotactic space and segmenting brain tissues into gray matter (GM), white matter (WM), and cerebrospinal fluid images for statistical analyses. As opposed to ROI-based method, VBM detects structural differences within the entire brain and can be applied in large cohorts to identify patterns of structural abnormality. The development of surfaced-based morphometry (SBM) is a further step, allowing for analyses of complementary surface measurements such as cortical thickness, area, volume and curvature. Both VBM and SBM can be performed using automatic software programs such as statistical parametric mapping (SPM) and FreeSurfer. They provide standardized pipelines with adjustable parameters, generating statistical results with high reproducibility.

### *IR and Volumetric Alterations*

Volumetric analyses of the brain structures in patients with IR started as early as in the 2003 (Table 1), ever since the increased risk of dementia has been noticed in diabetics. The study performed by Heijer et al adopted a hypothesis-driven approach, investigating the association between diabetes mellitus, IR, and the degree of hippocampal and amygdalar atrophy in 506 participants.[31] Images were collected on 1.5 T MR with a custom-made 3D sequence (half-Fourier acquisition single-shot turbo spin echo) and ROIs were set through manual tracing. Results showed that subjects with diabetes mellitus had smaller hippocampal and amygdalar volumes, but the negative correlation between IR index and amygdala volume was only found in nondiabetic participants. Another early study published in 2003 also addressed the atrophy of medial temporal structure, but in a small sample size of 30 healthy subjects.[32] In this study, images were collected on 1.5 T MR using 3D spoiled gradient recalled sequence and hippocampus was also manually outlined. Although individuals with higher glucose levels had significantly smaller

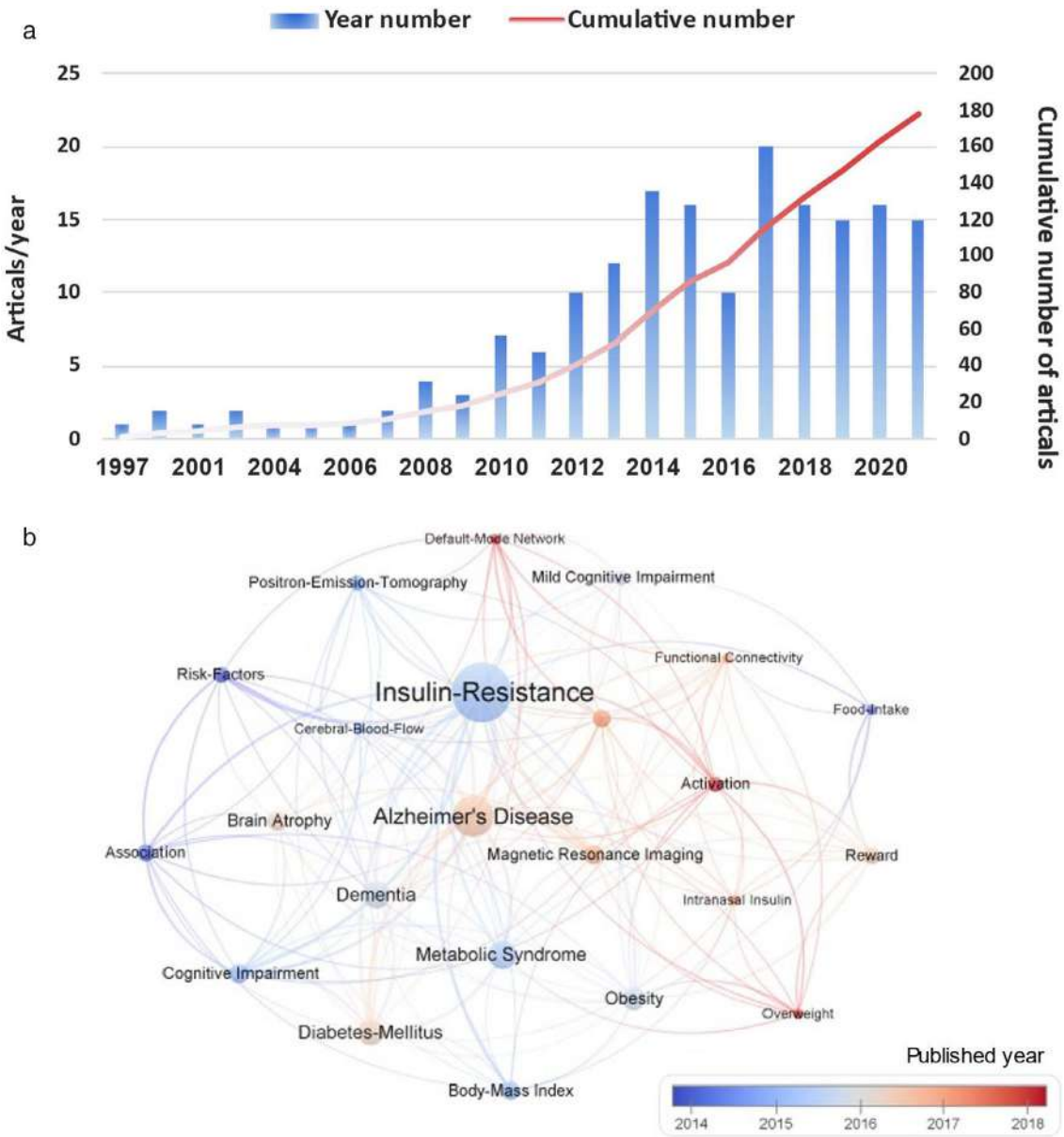


**FIGURE 2: The number and keywords distribution map of the relevant articles. (a) Studies began as early as 1997, which investigated the relation between IR and silent infarction on conventional MRI. Since 2010, there is an increase in publication that peaked in 2017, and the number were stable in recent years. (b) Keywords distribution map generated by VOSviewer software (www.vosviewer.com). It indicates that studies on IR are closely connected with AD, dementia, metabolic syndrome and MRI. Displayed by published year (later in red), it is clearly shown that MRI studies, especially those on brain activation, memory and reward, functional connectivity, default-mode network and brain atrophy are more concentrated since 2016.**

hippocampi and worse performance in recall test, insulin level did not show direct relationship with the hippocampal volumes. These two studies adopted similar ROI-based analyses, both focusing on medial temporal lobe, but the associations between volumetric changes and IR level were inconsistent. These inconsistencies might be caused by the prominent differences in sample size and the inevitable bias in manual tracing of the ROIs.

*HEALTHY SUBJECTS.* Since then, numerous volumetric MRI studies have explored the relationship between IR and cognitive impairment, using ROI-based methods and, more recently, VBM, with a particular interest on medial temporal lobe. Representatives are studies that investigated healthy or asymptomatic adults, which avoided the confounding factors of MetS (Table 1). In a study consisted of 50 healthy and cognitively intact middle-aged women, the authors again focused on the hippocampal integrity through manual tracing. Results demonstrated a significant negative relationship between IR index and right and total hippocampal volume, and overall cognitive performance.[33] In another study comprising 285 healthy elderlies, VBM was adopted to determine

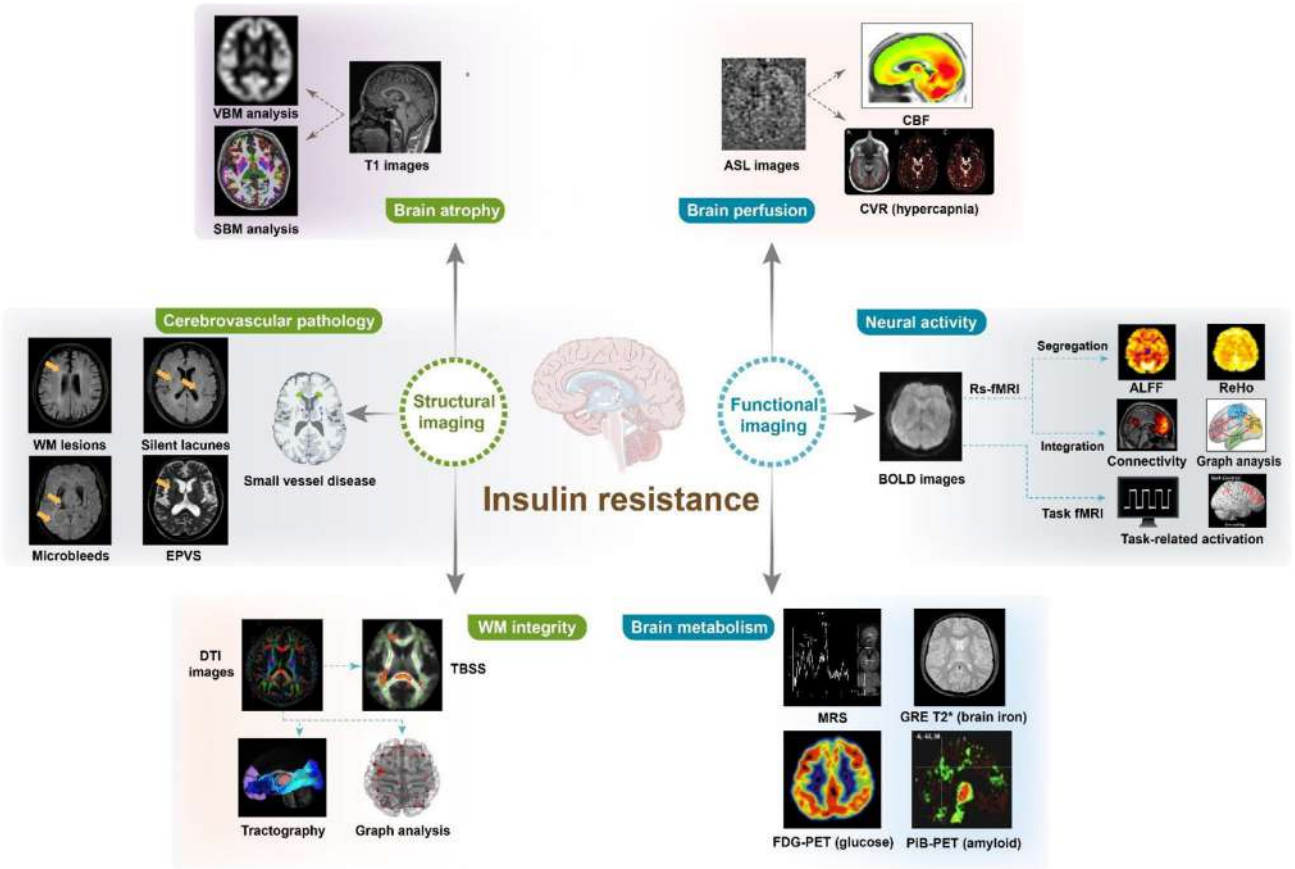


**FIGURE 3: Overview of the main imaging techniques included in the current review. These techniques can be broadly divided into structural and functional imaging. Conventional imaging is frequently used to evaluate brain atrophy and small vessel disease, but with innovations in analytical methods such as VBM and SBM analysis, and automatic lesion segmentation. More advanced techniques enable to assess WM microstructure, neural activity/connectivity, perfusion, and metabolism. Graph analysis is frequently applied on DTI and BOLD images to assess the brain topology and efficiency. *Source*: Images representing CVR, task-fMRI, and amyloid deposition are from references 28–30, respectively. Permissions of image usage have been obtained from the publishers. VBM = voxel-based morphometry; SBM = surfaced based morphometry; WM = white matter; CVR = cerebrovascular reactivity.**

the voxel-wise correlations between brain volume, insulin sensitivity and cognitive performance. IR index was found to be negatively correlated with total brain size and the consistent temporal volume, which were known to be involved in speech production.[34] In a 4-year longitudinal study using VBM, 372 middle-aged healthy participants at baseline and 121 individuals at follow-up were included. Higher IR level was related to less GM volume at baseline and 4 years later in multiple regions susceptible to AD, especially the medial temporal lobe that is responsible to encode episodic information.[35] In a large cohort study including 186 original and 1867 offspring cohorts, lower circulating IGF-1 levels, the precedent of IR development, was associated with lower total brain volume. Although hippocampus was set as a particular ROI through manual tracing, no direct correlation was found between IGF-1 level and hippocampal volume.[36]

*NEURODEGENERATIVE DISEASES.* In cognitive impaired or neurodegenerative patients, results regarding the relationship between IR and brain atrophy are mixed, suggesting such relationship might be disease specific (Table 1, brain volume). For example, Burns et al investigated the relationship between IR and brain atrophy as assess by VBM in early AD ($n = 48$) and nondemented controls ($n = 61$). Interestingly, higher baseline insulin level was associated with 2-year decline in brain volume in controls, but the relationship was inverse in AD patients. In early AD, higher insulin level was associated with less volumetric loss in bilateral hippocampi and cingulate cortices, demonstrating an AD-specific benefits of preventing cerebral atrophy.[37] Similarly, another VBM study with smaller sample size also demonstrated disease-specific directionality of the relationship. By recruiting healthy elderly control ($n = 21$), AD ($n = 20$), and Parkinson's disease ($n = 22$) patients, the authors observed negative correlation between IR and GM volume in both HC and AD subjects, but the relationship was positive in PD (increased IR with increased volume)[38] (Fig. 4). Although there is inconsistency regarding the relationship

**TABLE 1. Overview of Neuroimaging Abnormalities Associated With Insulin Resistance**

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| Brain volume | | | | | | |
| 31, 2003 | T1WI | ROI: hippocampus, amygdala (manual tracing) | 506 healthy adults | 73 ± 8 | Smaller hippocampal and amygdalar volumes in diabetics | More amygdala atrophy, but only in nondiabetics |
| 32, 2003 | 3D-T1WI | ROI: hippocampus, parahippocampal and superior temporal gyrus | 30 healthy adults | 68.6 ± 7.5 | Smaller hippocampi in individuals with higher blood glucose levels | Not related to cognitive performance, age or brain volumes |
| 33, 2011 | 3D-T1WI | ROI: hippocampus (manual tracing) | 50 healthy and cognitively-intact women | 57.4 ± 4.3 | / | More hippocampal atrophy and worse overall cognitive performance |
| 34, 2012 | 3D-T1WI | Voxel-wise: VBM | 285 cognitively healthy controls | 75 years | / | Negative correlation with bilateral temporal and total brain volume, and performance in verbal fluency |
| 35, 2013 | 3D-T1WI | Voxel-wise: VBM ROI: hippocampus and parahippocampus | Baseline: 372 participants 4-year follow-up: 121 participants | Baseline: 57.6 ± 7.5 | / | Atrophy in cingulate cortices, medial temporal lobe, prefrontal gyri at baseline and follow-up, particularly medial temporal lobe |
| 36, 2014 | T1WI (4 mm thickness) | Total brain volume ROI: hippocampus | 186 original cohorts and 1867 offspring cohorts | Original: 77 ± 3 Offspring: 61 ± 9 | / | Lower IGF-1 level (precedent of IR) was associated with lower total brain volume in both generations |
| 37, 2012 | 3D-T1WI | Voxel-wise: VBM | Baseline and 2-year follow-up: 48 early AD and 61 | AD: 73.3 ± 6.7 Controls: 75.2 ± 6.3 | Lower baseline brain volume, greater cognitive decline and brain atrophy in AD | Controls: higher baseline insulin level was associated with 2-year decline in global cognitive performance |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | nondemented controls | | | Early AD: higher baseline insulin was associated with less decline in cognitive performance, and less atrophy in hippocampi and cingulate cortices |
| 38, 2014 | 3D-T1WI | Voxel-wise: VBM | 21 healthy controls<br>20 AD patients<br>22 PD patients | Controls: 71.7 ± 6.2<br>AD: 72.4 ± 5.1<br>PD: 71.0 ± 5.7 | / | Controls and AD: negative correlation with volume in medial prefrontal and medial temporal lobe<br>PD: positive correlation with parietal volume |
| 39, 2021 | 3D-T1WI | Voxel/Vertex-wise: VBM and SBM | 973 participants (104 with MetS and 869 without) | 52.5 ± 13.6 | / | IR in MetS was associated with reduction in cortical volume and thickness (precentral cortex, temporal cortex, and cuneus) |
| 40, 2020 | 3D-T1WI | ROI-wise: SBM | 533 healthy adults | 36–65 years | / | IR in females over 50 years was associated with lower cortical thickness in lateral frontal, parietal and the superior temporal cortex |
| 41, 2018 | 3D-T1WI | Whole brain volume | 46 depressed and overweight youth | 14.82 ± 1.95 | / | Insulin sensitivity was positively correlated with whole brain volume |
| 42, 2019 | 3D-T1WI<br>BOLD fMRI | Cortical thickness and FC (seeds: ACC and hippocampus) | 42 depressed and overweight youth | 14.82 ± 1.86 | Patients with greater IR had reduced hippocampal and ACC volumes, and greater dysconnectivity in fronto-limbic reward networks | Negative correlation with hippocampal connectivity |
| Cerebrovascular pathology | | | | | | |
| 43, 2019 | | CSVD score: sum of WMH, EPVS, | 156 healthy adults | IR: 67.45 ± 5.92 | Higher proportion of lacunar, CMB and EPVS in IR group | |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | T1WI, T2WI, FLAIR, DWI, SWI | CMB and lacunes | | Non-IR: 70.03 ± 7.30 | | Positive dose-dependent correlation with total CSVD score |
| 44, 2015 | T1WI, T2WI, FLAIR | WMH and incident lacunes | Baseline and 10-year follow-up: 934 participants | MetS: 55.8 ± 4.5 Non-MetS: 56.0 ± 4.2 | MetS persons had more incident lacunes, but no difference in WMH progression | Correlated with incident lacunar disease but not WMH progression |
| 45, 2016 | T1WI, T2WI, FLAIR | Silent lacunes and WMH volume | 2326 adults | 56.2 ± 9.0 | The proportion of subjects with IR and IR level was higher in the lacunar group | Independently associated with the presence and severity of lacunes, but not WMH volume |
| 46, 2010 | T2WI, FLAIR | WMH scoring | 105 stroke patients without diabetes | HOMA-IR ≥ 2.5: 67.6 ± 7.8 HOMA-IR < 2.5: 70.5 ± 10.0 | IR level was higher in patients with higher grading of WMH lesions | Positively correlated with WMH grades regardless of location |
| 47, 2018 | Ultrasonography | IMT and stenosis of common carotid artery | 4816 nondiabetic subjects | 50–65 years | IMT and stenosis were more severe in insulin resistant subjects | Associated with increased IMT after adjustment for age and sex |
| 48, 2010 | T1WI, T2WI, FLAIR | WMH presence | 102 T2DM patients | WMH-negative: 58 ± 6 WMH-positive: 59 ± 6 | IR index was higher in WML-positive group than the negative group | Independent risk factors for WMH presence in T2DM |
| WM microstructure | | | | | | |
| 49, 2014 | DTI | TBSS analysis | 127 healthy subjects | High IR: 62.14 ± 10.31 | Group with higher IR showed decreased FA and axial diffusivity throughout the cerebral WM | Negatively correlated with axial diffusivity, especially in CC and corona radiata |

**TABLE 1. Continued**

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | | Low IR: 62.50 ± 11.46 | | |
| 50, 2019 | SPGR and balanced SSFP | Myelin content | 145 cognitively unimpaired adults | 61.4 ± 6.2 | / | Negatively associated with MWF in parieto-occipital, posterior thalamic radiation, superior occipital gyrus and cuneal regions |
| 51, 2017 | 3D-T1WI DTI | Voxel-wise: VBM and TBSS analysis | 15 T2DM patients 21 obese adolescents 22 healthy controls | 12–18 years old | Smaller volume in T2DM and obese, especially in medial brain regions; decreased FA in T2DM | Independent predictor of decreased FA in T2DM |
| 52, 2020 | DTI | Tractography (cingulum bundle) | 37 T2DM patients 34 healthy controls | T2DM: 59.7 ± 7.3 Controls: 56.9 ± 6.1 | T2DM showed decreased FA and increased MD in the right cingulum, and lower FA and shorter fiber length in the left cingulum | IR in T2DM group was negatively correlated with the mean length of the cingulum |
| 53, 2018 | DSI | Tractography (uncinate fasciculus and superior cingulum bundle) | 27 T2DM patients 21 healthy controls | T2DM: 60.6 ± 7.6 Controls: 56.1 ± 7.8 | T2DM patients showed decreased FA in the left uncinate fasciculus and right superior cingulum bundle | / |
| 54, 2022 | DTI BOLD-fMRI | Interhemispheric functional and structural connectivity | 38 T2DM patients 42 healthy controls | T2DM: 60.2 ± 7.4 Controls: 58.2 ± 6.4 | T2DM patients showed lower FC between bilateral lingual gyrus and sensorimotor cortex, and lower FA and shorter length of fibers linking bilateral lingual gyrus | Negatively correlated with the length and FA value of fibers linking bilateral lingual gyrus |
| 55, 2022 | DTI | Graph analysis | 44 T2DM patients 34 healthy controls | T2DM-MCI: 62.1 ± 5.9 T2DM-NC: 60.2 ± 6.6 | T2DM-MCI group showed widely reduced nodal efficiency | / |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | | HC: 60.6 ± 5.4 | | |
| Neural function | | | | | | |
| Functional segregation | | | | | | |
| 56, 2014 | BOLD | ALFF and ReHo | 29 T2DM patients 27 healthy controls | T2DM: 58.3 ± 7.3 Controls: 57.8 ± 5.9 | T2DM patients showed decreased ALFF and ReHo values in the occipital lobe and parietal regions | HOMA-IR in T2DM was negatively correlated with ReHo values in the cuneus |
| 57, 2013 | BOLD | ALFF | 28 T2DM patients 29 healthy controls | T2DM: 58.7 ± 8.1 Controls: 57.7 ± 7.2 | T2DM patients showed decreased ALFF values in bilateral middle temporal gyrus and occipital regions | Insulin secretion in T2DM was positively correlated with the ALFF value in the middle temporal gyrus |
| 58, 2019 | BOLD | fALFF and ReHo | 19 T2DM-PDN 18 T2DM patients non-DPN 15 controls | T2DM-PDN: 53.8 ± 8.1 T2DM-N: 54.1 ± 6.9 Controls: 53.9 ± 5.4 | T2DM-PDN showed decreased fALFF values in somatosensory, cognitive, emotional and pain-related brain regions | IR in T2DM-PDN was negatively correlated with fALFF in occipital lobe; IR in T2DM-N was negatively correlated with fALFF in postcentral gyrus |
| Functional integration | | | | | | |
| 59, 2012 | BOLD | Seed-based FC centered on ventral striatum | 90 healthy adults | 40.4 ± 6.4 | / | Related to increased connectivity between ventral striatum and anterior mid-cingulate cortex, and predicted depressed mood |
| 60, 2018 | BOLD | Seed-based FC centered on caudate; Graph analysis | 18 healthy adults | 50.1 ± 4.9 | Individuals with greater IR showed higher connectivity within reward networks and lower centrality in cingulate cortex following a meal | Negatively associated with eigenvector centrality in the dorsal anterior cingulate cortex following a meal |
| 61, 2012 | BOLD | Independent component Analysis | 11 lean young adults 12 obese young adults | Lean: 23.5 ± 2.1 Obese: 24.7 ± 2.4 | Obese showed altered FC strength in the DMN and temporal network | Insulin sensitivity negatively correlated with FC in food and reward processing networks |

**TABLE 1. Continued**

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| 62, 2013 | BOLD | Seed-based FC centered on DMN | 20 healthy women | Higher insulin: 59.2 ± 57.1 Lower insulin: 57.1 ± 4.2 | Higher-insulin group showed reduced DMN-hippocampal connectivity | / |
| 63, 2017 | BOLD | Graph analysis; ALFF | Baseline: 80 MCI and 127 controls 35 m follow up: 50 MCI and 60 controls | MCI: 69.53 ± 7.43 Controls: 68.88 ± 6.67 at baseline | MCIs showed disconnections in brain networks of IR-related genes, mainly in the cerebellum-frontal-temporal regions | Influenced the overall efficiency of brain functional networks |
| 64, 2013 | BOLD | Seed-based FC centered on PCC | 10 T2DM patients 11 healthy controls | T2DM: 56 ± 2.2 Controls: 54 ± 1.8 | T2DM patients showed decreased FC between PCC and middle temporal gyrus, medial frontal gyri, and the left thalamus | HOMA-IR in T2DM inversely correlated with FC of PCC-inferior frontal gyrus and PCC-precuneus ($n = 5$) |
| 65, 2013 | BOLD | Seed-based FC centered on PCC | 30 T2DM patients 31 healthy controls | T2DM: 59.0 ± 7.9 Controls: 57.2 ± 6.9 | T2DM patients showed decreased FC between PCC and middle temporal gyrus, occipital and precentral regions | HOMA-IR in T2DM negatively correlated with FC of PCC-middle temporal gyrus |
| 66, 2015 | BOLD | Interhemispheric connectivity | 32 T2DM patients 30 healthy controls | T2DM: 59.5 ± 8.2 Controls: 56.2 ± 7.1 | T2DM patients showed abnormal interhemispheric FC, particularly in the middle temporal regions | IR in T2DM was negatively correlated with FC of bilateral middle temporal gyrus |
| 67, 2015 | BOLD | Independent component analysis | 42 T2DM patients 42 healthy controls | T2DM: 60.4 ± 7.0 Controls: 58.2 ± 6.3 | T2DM showed increased connectivity in the anterior DMN and decreased connectivity in the posterior DMN | Negatively correlated with connectivity in posterior DMN |
| Task fMRI | | | | | | |
| 68, 2019 | BOLD | Two-back working memory task | Nine healthy adults | 64.9 ± 7.7 | | |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | | | Insulin infusion induced an increase in the spatial extent and strength of task-related signals | Insulin sensitivity was positively related to the degree of task-related activation |
| 69, 2011 | BOLD | Two-back working memory task | 19 MetS patients 21 healthy controls | MetS: 50.4 ± 5.3 Controls: 47.4 ± 6.0 | MetS individuals demonstrated lower task-related BOLD response | / |
| 28, 2017 | BOLD | Episodic memory task | 17 obese adults 17 lean adults | Obese: 27.7 ± 5.7 Lean: 27.3 ± 5.9 | Higher IR showed reduced activation throughout the core recollection network | / |
| 70, 2014 | BOLD | Encoding and recognition tasks | 22 T2DM patients 29 healthy controls | T2DM: 56.0 ± 5.5 Controls: 52.7 ± 5.5 | T2DM showed reduced activation of task-relevant regions and less extensive deactivation of the DMN | HOMA-IR in controls was related to brain activation during recognition task |
| Cerebral perfusion | | | | | | |
| 71, 2016 | ASL and phase-contrast MR | CBF and arterial blood flow | 120 cognitively healthy adults | 57 ± 5 | / | Lower arterial blood flow in internal carotid arteries, and lower perfusion in frontal and temporal lobe regions |
| 72, 2014 | ASL | CBF | 23 T2DM patients 27 IR patients 37 healthy controls | T2DM: 54.2 ± 5.2 IR: 50.9 ± 4.5 Controls: 51.8 ± 3.8 | IR patients showed lower mean cortical CBF than T2DM patients | / |
| 73, 2017 | ASL | CBF | Baseline: 41 T2DM and 32 controls | T2DM: 65.5 ± 8.3 Controls: 67.3 ± 10.1 | T2DM patients showed decreased CBF in the DMN, visual, and cerebellum networks at baseline, but no group difference at follow-up | Greater decrease in longitudinal CBF values |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | 2-year follow-up: 19 T2DM and 23 controls | at baseline | | |
| 74, 2017 | ASL | CBF | 40 T2DM patients 41 healthy controls | T2DM: 60.5 ± 6.9 Controls: 57.9 ± 6.5 | T2DM had decreased CBF in PCC, precuneus and bilateral occipital lobe | More hypoperfusion in PCC and precuneus |
| 75, 2010 | Transcranial Doppler | Increase in blood flow to hypercapnia | 83 cerebrovascular patients | MetS: 60 ± 14 No MetS: 58 ± 18 | MetS was associated with lower vasomotor reactivity adjusting for stenosis and stroke | / |
| 29, 2017 | ASL | CBF increase to hypercapnia | 60 cognitively normal | Obese with IR: 53.3 ± 4.3 Obese w/o IR: 50.7 ± 3.2 Lean controls: 51.8 ± 4.9 | Obese participants had lower CVR to hypercapnia than lean controls | Insulin sensitivity in obese subjects with IR was correlated with higher CVR after accounting for BMI |
| Brain metabolism | | | | | | |
| 76, 2015 | FDG-PET | Glucose uptake | 150 normal adults | 60.7 ± 5.8 | / | Lower total brain and regional glucose metabolism, especially in the left medial temporal lobe |
| 77, 2011 | FDG-PET | Glucose metabolic rate | 23 newly diagnosed diabetes 6 controls | 74.4 ± 1.4 | Diabetic subjects showed more widespread activation during a memory encoding task compared with controls | Hypometabolism in frontal, parietotemporal, and cingulate regions in diabetic adults |
| 78, 2015 | FDG-PET | ROI-based: glucose uptake in AD-vulnerable regions | 194 MCI 60 AD 26 controls | MCI: 75.2 ± 7.3 AD: 75.2 ± 7.3 | Lower metabolism in a stepwise manner from CN to MCI to AD in global, parietal, and hippocampus | Hypermetabolism in MCI-progressors and hypometabolism in AD in medial temporal regions |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| | | | | Controls: 75.7 ± 5.7 | | |
| 30, 2015 | PiB-PET | ROI-based: amyloid deposition in frontal, parietal and temporal | 186 adults | 60.4 ± 5.6 | / | Higher amyloid deposition in frontal and temporal areas |
| 79, 2014 | GRE sequence | Brain and liver iron load | 23 obesity 20 controls | Obesity: 50.4 ± 7.7 Controls: 48.8 ± 9.5 | Obese subjects showed higher iron load in caudate nucleus, lenticular nucleus, hypothalamus, hippocampus, and liver | Higher iron load in caudate, hippocampus, and liver |
| 80, 2015 | SPECT PiB-PET | CBF Amyloid deposition | 29 AD 18 diabetes-related dementia | AD: 76.8 ± 5.6 Diabetes-related dementia: 80.3 ± 3.6 | Less follow-up CBF reduction in diabetes-related dementia group than the AD group | / |
| 81, 2020 | $^{1}$H-MR spectroscopy | Prefrontal NAA and creatine | 50 T2DM with obesity 50 T2DM without obesity 50 controls | T2DM with obesity: 49.0 ± 7.4 T2DM without obesity: 49.3 ± 8.1 Controls: 49.0 ± 7.8 | T2DM-obesity groups showed lower prefrontal NAA than controls | Lower prefrontal NAA levels in the T2DM-obesity group but not in the T2DM group |
| IR-targeting treatments | | | | | | |
| Intranasal insulin | | | | | | |
| 82, 2013 | BOLD ALFF | Voxel-wise: fALFF | 17 healthy females | 24.5 ± 2.2 | Increased brain activity in the hypothalamus and orbitofrontal cortex | / |

TABLE 1. Continued

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| 83, 2014 | ASL | CBF | 48 healthy males | 24.0 ± 3.4 | CBF increase in the insular cortex and putamen | / |
| 84, 2012 | BOLD | Voxel-wise: fALFF | 12 healthy subjects | 28 ± 9 | Increased fALFF in hypothalamic activity and decreased IR index | Decreased IR index was correlated with fALFF values in the putamen, right insula and orbitofrontal cortex |
| 85, 2019 | BOLD | Seed-based FC centered on midbrain (VTA and SN) | 19 normal weight<br>17 overweight | Normal weight: 29.5 ± 4.6<br>Overweight: 27.8 ± 4.5 | Time- and dose-dependent effects on the FC between midbrain and prefrontal cortex | The effects of intranasal insulin varied with preexisting insulin sensitivity |
| 86, 2012 | $^{31}$P MR spectroscopy | Cerebral energy metabolism | 15 healthy males | 24.6 ± 1.3 | Increased cerebral high-energy phosphate content compared with placebo administration | / |
| 87, 2014 | ASL | Perfusion change to hypercapnia | 15 T2DM patients<br>14 healthy controls | T2DM: 62.0 ± 7.9<br>Controls: 60.1 ± 9.9 | T2DM patients showed a greater perfusion increase in the insular cortex | / |
| 88, 2015 | BOLD | Seed-based FC centered on hippocampus | 14 T2DM patients<br>14 healthy controls | T2DM: 61.7 ± 8.1<br>Controls: 60.1 ± 9.9 | Insulin on T2DM patients induced increases in FC between hippocampus and multiple DMN regions | / |
| 89, 2012 | FDG-PET | Cerebral glucose metabolism | 64 MCI patients<br>40 AD patients | Placebo: 74.9 ± 1.6<br>20 IU treatment: 72.8 ± 1.5<br>40 IU treatment: 69.9 ± 1.4 | Insulin-treated patients showed no significant decline in glucose uptake during the 4 m follow-up, while placebo-treated showed diffusely decreased glucose uptake | / |

**TABLE 1. Continued**

| References, year | Imaging Techniques | Analytic Methods | Study Groups | Age (mean ± SD) | Group Differences | IR Correlations |
|---|---|---|---|---|---|---|
| 90, 2021 | T2WI, FLAIR | WMH and GMV | 49 participants | 55–85 years | 12 m treatment induced decrease in WMH volume in deep and frontal regions, with a similar trend for global volume | / |
| Other treatments | | | | | | |
| 91, 2015 | 3D-T1WI | Vertex-wise: SBM | 11 T2DM patients 11 healthy controls | T2DM: 47–75 years Controls: 46–65 years | T2DM patients showed cortical thinning at baseline and cortical thickening after 1 year of insulin therapy | / |
| 92, 2013 | $^{1}$H-MRS | NAA, Cho, Cr, myo-inositol and Glx | 16 healthy men | | Increased NAA and Glx, and decreased Cho and myo-inositol, but only in insulin-sensitive subjects | Insulin sensitivity correlated with the altered metabolites measurements |
| 93, 2002 | FDG-PET | Glucose uptake | Eight healthy males | 49.3 ± 5.1 | Increased global glucose metabolism, mainly in the cerebral cortex | / |
| 94, 2001 | $^{1}$H-MRS | Glucose (peak at 5.23 ppm) | Seven healthy subjects | 30 ± 2 | No effect on the glucose concentration in occipital cortex | / |
| 95, 2016 | FDG-PET PiB-PET | Glucose uptake Amyloid deposition | 38 AD patients | 55–80 years | 26 weeks treatment prevented the decline of glucose metabolism, but showed no effect on cognition or Aβ burden | / |

VBM = voxel-based morphometry; SBM = surfaced-based morphometry; IR = insulin resistance; HOMA-IR = homeostasis model assessment of insulin resistance; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; FC = functional connectivity; T2DM = type 2 diabetes mellitus; CSVD = cerebral small vessel disease; WMH = white matter hyperintensity; EPVS = enlarged perivascular space; CMB = cerebral microbleed; MetS = metabolic syndrome; TBSS = tract-based spatial statistics; BOLD = blood oxygen level-dependent; ALFF = low-frequency fluctuations; fALFF = fractional ALFF; ReHo = regional homogeneity; PDN = diabetic neuropathy; DMN = default-mode network; MCI = mild cognitive impairment; CVR = cerebrovascular reactivity; IMT = intima-media thickness; SPGR = spoiled gradient echo; MWF = myelin water fraction; FA = fractional anisotropy, PiB = Pittsburgh Compound B; GRE = gradient echo sequences; MI = myo-inositol; VTA = ventral tegmental area; SN = substantia nigra.

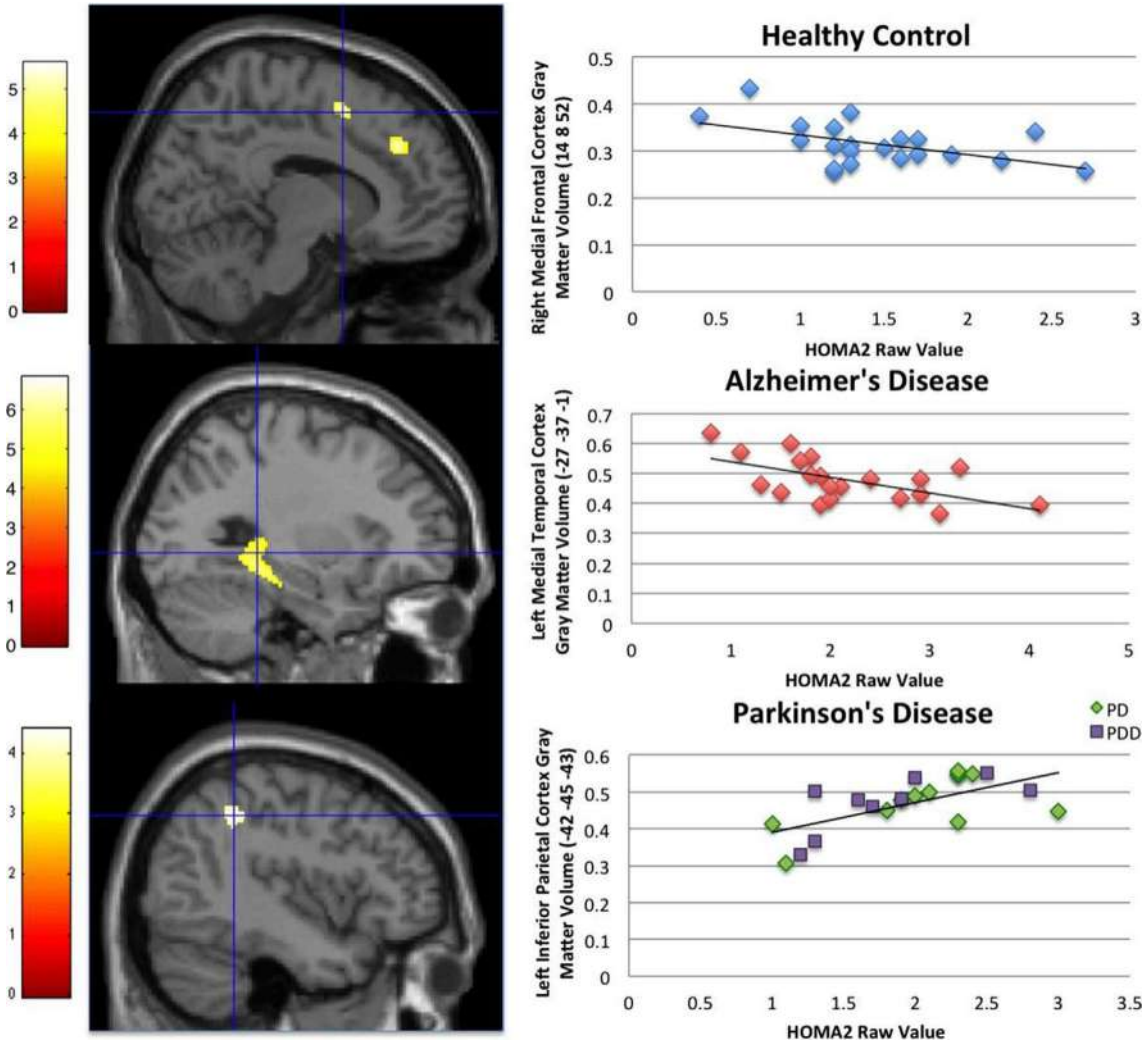


**FIGURE 4: Relationship between higher HOMA2, an indication for insulin resistance, and regional gray matter volume (GMV) in healthy control, AD, and PD individuals. In HC subjects, increased HOMA2 was associated with less volume in the right medial frontal cortex. In AD subjects, increased HOMA2 was associated with less GMV in the hippocampus/parahippocampus, as well as the postcentral gyrus, inferior temporal cortex, fusiform gyrus, and cerebellum. Conversely, individuals with PD who had increased HOMA2 exhibited higher GMV than those with lower HOMA2 in the left inferior parietal region. These results suggested that the relationship between IR and GMV might be disease specific.** ***Source*****: Image from reference 38 by permission of Elsevier. HOMA2 = homeostasis model assessment of insulin resistance 2; AD = Alzheimer's disease; PD = Parkinson's disease.**

between IR and brain volume across studies. These results provided valuable information that IR may impact the brain differently in normal aging and neurodegenerative disease, which can be explained by the differences in pathological processes, severity of metabolic dysregulation, or a combination of both factors.

*METABOLIC SYNDROME.* Brain atrophy in metabolic syndrome (MetS) (including obesity, impaired glucose metabolism, elevated blood pressure, and dyslipidemia) has been widely reported. While MetS is likely to result from a complex interplay, IR is thought to be central in its pathogenesis and account for alterations in brain structure.[101] In a recent large-scale population-based study, comprehensive VBM and SBM analyses were performed on 973 participants using FreeSurfer software. Acquired on 3 T MR, images were processed and volumetric measures including total volume, GM and WM volume, and cortical thickness were obtained. Results indicated that IR was associated with smaller cortical GM volume and thickness but not with WM or subcortical volume. Importantly, the effect of MetS on brain structure substantially overlapped with that of IR, indicating that IR might be a main contributor for MetS-related cortical atrophy.[39] Similar effects of IR on cortical thinning were also reported by Shin and colleagues in a sample of over 500 participants.[40] Adiposity-related IR was found to be associated with lower cortical thickness across the globe, with the strongest associations locating in the lateral frontal, parietal, and superior temporal cortices. In a group of 46 depressed and obese children, whole brain volume was calculated using

VBM and was positively correlated with insulin sensitivity independent of age, sex, depression severity, and several other clinical factors.[41] In addition, these teenager patients with greater IR index also showed reduced hippocampal and anterior cingulate cortex (ACC) volumes, which were associated with more severe depressive symptoms.[42] These results in teenager studies provided additional information that insulin also play important roles in developing brain and emotional behaviors.

Pertaining to T2DM that is characterized of IR, the reduction in GM volume and cortical thickness were more extensively reported. However, most T2DM studies attributed the volumetric changes to glycemic dysregulation, dyslipidemia and accompanying vasculopathy. Therefore, the morphological alterations in T2DM are attributed to IR per se or an interplay of endocrine and cardiovascular risk factors are still unclear.

## Cerebrovascular Disease

### *Methodological Review*

Cerebral small vessel disease (CSVD) is a broad category of pathological processes that affect the small arteries, arterioles, venules, and capillaries of the brain. CSVD is a frequent accompaniment of aging and neurodegenerative disease, and can exacerbate cognitive deficits, physical disabilities, and other symptoms of neurodegeneration.[102] It is also suggested as the most common vascular cause of dementia and a major contributor to mixed dementia. The symptoms of CSVD vary from asymptomatic occurrence to various neuropsychological symptoms, mainly including stroke, cognitive deficits, psychiatric disturbance, and physical disabilities. Given the close link between CSVD and cognitive ability, early recognition of CSVD in clinical practices has been increasingly noticed as important strategy for dementia diagnosis and treatment.

Neuroimaging consensus standards for classification of CSVD were first proposed in 2006 and have been incorporated as part of the criteria for vascular dementia.[103] According to the international neuroimaging consensus standard for MRI (known as STRIVE recommendation),[102] CSVD include recent small subcortical infarcts (RSSI), lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), microbleeds, and brain atrophy. RSSI is defined as small (≤20 mm in diameter) hyperintensity on DWI. Lacune is a subcortical fluid-filled cavity of 3–15 mm in diameter. WMH shows hyperintensities on FLAIR/T2WI without cavitation and commonly distribute in the deep brain and periventricular regions. EPVS is CSF-like lesions without hyperintense rim on T2WI/FLAIR. Cerebral microbleeds are small (2–10 mm) hypointensity best seen on T2*/SWI. Atrophy indicates a lower brain volume that is not related to macroscopic focal injury such as trauma or infarction. These imaging markers are present in about 10% of patients in their seventh decade rising to above 85% of those in their ninth decade.[104] Some of the recent studies have applied computational methods to automatically quantify CSVD lesions, based on machine learning-based algorithms such as support vector machines (SVMs) and random forest. But the application of these methods to clinical research is still premature.

### *IR and CSVD*

*HEALTHY SUBJECTS.* Emerging studies have recognized the adverse impact of IR on vascular pathology, probably through promoting endothelial dysfunction and atherosclerosis.[105] Imaging studies have investigated the relationship between IR and CSVD using MRI (Table 1). In a study comprising 156 elderly nondiabetic population, total CSVD score was calculated on conventional MRI metrics as the sum of WMH, cerebral microbleeds, lacunes, and enlarged perivascular spaces, ranging from 0 to 4. Results suggested that increased IR independently predicted the increased burden of overall CSVD in a dose-dependent manner,[43] but the relationship with individual SVD feature was not investigated. In another study including 934 participants, incident lacunes and WMH, and their progression during a 10-year follow-up were assessed using either visual rating or automated segmentation. Interestingly, IR was associated with incident lacunar disease but not WMH progression, implying that different CSVD lesions might have unique risk factors profiles.[44] Consistent results regarding the link between IR and individual component of CSVD were obtained in another large-cohort study on 2326 adults. Again, the authors found that IR was independently associated with both the presence and severity of lacunes, instead of the WMH volume.[45]

*OTHER DISORDERS.* In stroke patients, IR was found to be correlated with more severe burden of WMH and poorer functional outcome.[46,106] Comprising of 105 stroke patients without diabetes, the study visually evaluated the WMH by the Fazekas scale, dividing the lesions into periventricular and deep and subcortical WMH. Results showed that IR level was positively correlated with WMH grades regardless of location, even after adjusting for cardiovascular risk factors such as age and hypertension.[46] A large-cohort study of 4655 patients with acute ischemic stroke demonstrated that IR was related to a higher incidence of ischemic stroke and poorer functional outcome at 3 months after the stroke onset,[106] adjusted by age, sex, and stroke subtype and severity. Taken together, IR adversely impacts stroke probably through inducing hemodynamic disturbances and magnifying the role of risk factors, leading to the increased burden of WMH and poorer outcome. Furthermore, it might also contribute to the increased intima-media thickness in common carotid artery

and the development of atherosclerosis, as described in an ultrasonography study.[47]

There were also studies exploring the relationship between IR and SVD in T2DM patients, but results were mixed. In a study on 102 T2DM patients, IR index were significantly higher in WMH-positive group than the WMH-negative groups. The WM lesions were further independently predicted by the IR level, which implied the important role of IR in the pathogenesis of WMH in T2DM.[48] However, other types of SVD such as silent infarcts, microbleeds, and lacunar abnormalities were more frequently reported to be associated with the microcirculation, inflammatory markers, and ischemia caused by T2DM-induced vasculopathy, rather than IR.[107] Therefore, the cerebrovascular pathology in T2DM might be a multifactorial process and the independent effects of IR still need to be further clarified.

The above studies that investigated the relation between IR, brain atrophy, and cerebrovascular disease either utilized relatively rough global volumetric or macrostructural measures such as total brain/GM volume and WM hyperintensities, based on conventional sequences. These measurements cannot unravel more subtle abnormalities that underlie or precede the cognitive decline. Recently, more advanced sequences have been introduced to better characterize the neural activity, microstructural integrity, and vascular function, including but not limit to functional MRI (fMRI), DTI, and ASL. These additional techniques might capture more subtle changes in IR-related brain and will be discussed in the following sections separately.

## White Matter Microstructure Disruption

### *Methodological Review*

In neurodegenerative disorders, it is clear that cerebral WM, similar to cerebral cortex, also exhibits various types of degenerative changes that ultimately result in cognitive and functional decline.[108] Disruptions in WM microstructure in neurodegenerative conditions have been demonstrated, including decrease in density and volume of myelinated fibers.[109] Such changes in WM microstructure are suggested to be more sensitive than GM, at least during certain age span and in certain regions of the brain,[110] the assessment of which could reveal more subtle changes that precede brain atrophy and clinical manifestation. The advancement of MRI techniques has allowed the investigations into the altered patterns of WM microstructure. Generally, these MRI techniques use metrics derived from diffusion tensor imaging (DTI), or more advanced diffusion kurtosis imaging (DKI) and diffusion spectrum imaging (DSI), based on different diffusion acquisition schemes and models.[110] Generally, metrics derived from DTI include fractional anisotropy (FA) and mean, radial, and axial diffusivity, which are sensitive to cerebral microarchitecture such as local fiber density, coherence, orientation and myelination. DTI is by far the most widely used technique to assess WM microstructure, but it has insufficient ability to depict the multiple and crossing fiber bundles due to the limit of the tensor model. Alternative diffusion acquisitions and models have been therefore introduced, although have not been widely applied in the clinic yet. For example, diffusion spectrum imaging (DSI) enables more directions and higher b-values to better reflect the WM microstructure. Diffusion kurtosis imaging (DKI) measures deviations from the Gaussian signals, the parameters of which are analogous to those from DTI with additional mean, axial, and radial kurtosis. Besides, 3D fiber architecture could be reconstructed via tractography, allowing the visualization and quantification of the fiber bundles for further statistical analyses. With the advancement of analytical methods, structural connectivity based on diffusion data could be assessed using graph analysis to evaluate the topology, integrity, and efficiency of the structural network.[111]

### *IR and WM Disruptions*

*HEALTHY SUBJECTS.* The association between IR and WM integrity in generally healthy and cognitively intact adults have been investigated, but studies are limited (Table 1). In a study on 127 individuals aged 41–86 years old, participants were divided into high IR and low IR groups to compare their WM microstructure integrity based on DTI images. Voxel-wise comparison was performed using the tract-based spatial statistics (TBSS) embedded in the FSL software. According to the results, IR index was associated with decreased axial diffusivity (indication of axonal damage) broadly throughout the cerebral WM, independent of age, WMH volume, and antihypertensive medication status[49] (Fig. 5). In another study comprising 145 cognitively unimpaired adults, myelin water fraction (MWF), an advanced quantitative MR metric of myelin content, was acquired to reflect WMH integrity using spoiled gradient echo (SPGR) and balanced steady-state free precession (bSSFP) sequences and calculated through an in-house software. Higher IR was observed to be associated with lower MWF in parieto-occipital, superior occipital gyrus and cuneus WM, and the posterior thalamic radiations.[50] Such results provided direct evidence of the detrimental effects of IR on brain's myelin content, complementing DTI studies with more specific WM measurement.

*METABOLIC SYNDROME.* Numerous studies concentrated on the WM integrity in T2DM patients (Table 1). In a recent systemic review published in 2019, a total of 29 DTI studies were included that are all cross-sectional, varying in sample size, age range, and medication use.[112] Most articles (25/29) applied conventional DTI metrics, while three used graph theory and one used both. Among multiple brain

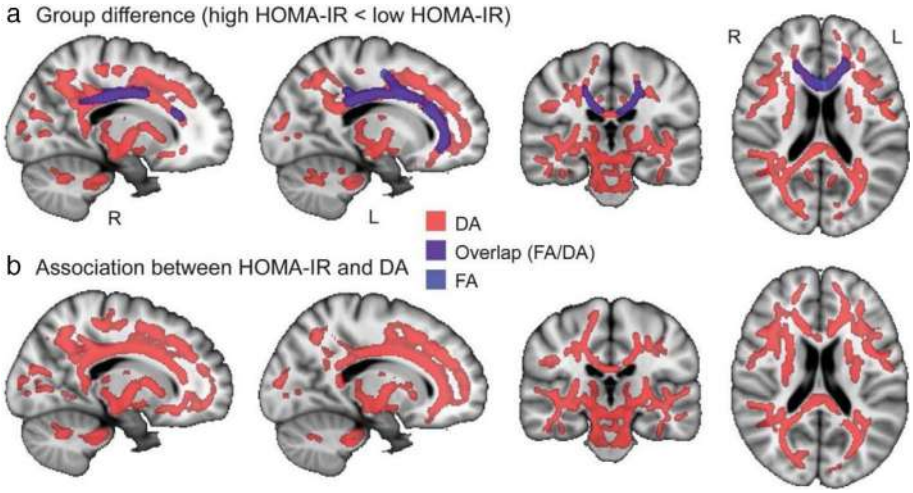


**FIGURE 5: TBSS maps of the effect of HOMA-IR on DTI parameters in middle-aged and older adults. (a) compared with the low HOMA-IR group ($n$ = 100), high HOMA-IR group ($n$ = 27) showed reduced DA (light red) and FA (light blue) in multiple brain regions. (b) Voxel-based association between DA and HOMA-IR in all participants. Light red indicates the regions where higher HOMA-IR is associated with lower DA. The statistical analyses were corrected for multiple comparisons, controlling for age, white matter signal abnormality volume, and antihypertensive medication status. TBSS = tract-based spatial statistics; DTI = diffusion tensor imaging; DA = axial diffusivity; FA = fractional anisotropy. *Source*: Image from reference 49 by permission of Wolters Kluwer Health, Inc.**

regions affected by T2DM, major WM tracts such as corpus callosum, cingulum, and corona radiata were more consistently demonstrated. However, only one study found the negative correlation between IR and FA values, showing that rather than BMI and HbA1c, HOMA-IR was the only independent predictor of decreased FA in T2DM patients and explained 8.1% of the variance.[51] Our very recent study added evidence of impairments in the cingulum bundle using diffusion tensor tractography, showing that T2DM patients exhibited decreased FA bilaterally, which were further correlated with elevated IR and worse performance in executive functioning.[52] In addition to conventional DTI, more advanced DSI has also been applied on T2DM patients, showing decreased FA in the left uncinate fasciculus and right cingulum bundle. But the study failed to investigate the correlation between insulin index and imaging metrics.[53] Other components of metabolic syndrome, such as obesity, hypertension, dyslipidemia, were all suggested to exert specific signature of WM microstructural abnormalities and accelerate cognitive decline, according to a comprehensive review.[113] However, the independent effect of IR was not displayed but only discussed as possible mechanism linking metabolic syndrome and cognitive impairment.

There are less studies that investigated WM connectivity or topology. Interhemispheric connectivity reflects the connection and information flow between the two hemispheres, which is an important indication for cognitive functioning. We recently explored the interhemispheric coordination in T2DM patients using an atlas-guided track recognition. Fibers linking bilateral regions were constructed and showed lower FA in occipital lobe, which were correlated with IR adjusting for age, sex, and education, even after multiple comparison correction.[54] Several other studies on T2DM patients reported decreased efficiency in the whole-brain WM network using graph theoretical analysis, but the direct relationship between IR and network metrics were not investigated.[55]

## Neuronal Dysfunction

### *Methodological Review*

As an energy-intensive organ, the brain is organized into different regions subspecialized for cognitive processes, which coordinate to maintain normal human behavior. Brain activity could induce changes in oxyhemoglobin and deoxyhemoglobin, which can be detected by sensitive blood oxygen level-dependent (BOLD) MR imaging. First introduced in 1990,[114] BOLD imaging relies on the paramagnetic properties of deoxyhemoglobin in blood, which increases in response to a surge of neural activity and result in the MR image intensity reduction. Functional MRI (fMRI) that relies on BOLD signal changes can thus be used to reflect neural activity and has been widely used to assess the functional architecture of the brain.[115] Generally, BOLD-fMRI includes resting-state fMRI (rs-fMRI) that focuses on spontaneous neural activity at res, and task-based fMRI that depicts the regions activated by a stimulus or task. As opposed to task-based fMRI, rs-fMRI does not require subjects to perform any specific task, during which the low-frequency oscillations of the signal will be captured to reflect the spontaneous neural activity. The lack of specific tasks is particularly convenient and rs-fMRI has been the mainstay technique in brain

research. There are a number of and kept growing analytic methods to analyze rs-fMRI data, which can be broadly divided into functional segregation (local activity of a specific region) and integration (connectivity between different regions). These analytic methods help investigators to locate the brain regions with altered neural activity and connections and to link these abnormalities with clinical parameters to explain the underlying mechanism. Although these methods have been validated for sensitivity, specificity, and reproducibility, results interpretation should be cautious due to massive amount of data and sophisticated processing procedure.[13]

## Resting-State Functional MRI

### *Functional Segregation*

Measurements that assess local neural activity usually include the amplitude of low-frequency fluctuations (ALFFs), a measure of spontaneous neuronal activity,[116] and regional homogeneity (ReHo), a measure of the neural regional synchronization.[117] Both ALFF and ReHo rely on BOLD signals within the low-frequency range between 0.01 and 0.1 Hz, which indicates the oscillations arise from spontaneous neuronal activity. ALFF calculates the total power and indexes the strength or intensity of oscillations, while ReHo evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbors.

There are few studies applying ALFF and ReHo on asymptomatic healthy subjects, but on patients with metabolic syndrome (Table 1). In our previous study, we combined the ALFF and ReHo approaches to examine the spontaneous fMRI signal oscillations and local synchronization in T2DM patients, using DPARSF software online based on standardized preprocessing. While the sample size is relatively small (29 patients), T2DM patients showed decreased neural activity in the parietal lobe, frontal lobe, middle temporal gyrus, and lingual gyrus. More importantly, the IR index was negatively correlated with the ReHo values in the cuneus, adjusting for structural differences and vascular risk factors such as hyperlipidemia, hypertension, and WMH.[56] Another study also adopted ALFF analyses in T2DM patients with similar sample size. The authors reported consistent findings of decreased ALFF values in the occipital lobe, with additional address on the temporal lobe. IR was correlated with temporal ALFF, but significance did not remain after multiple comparison correction.[57] Combined fractional ALFF (fALFF) and ReHo approaches were also applied in a specified subgroup of T2DM patients with painful diabetic neuropathy (PDN). The authors reported impaired neural activity in somatosensory, cognitive, and emotional regions that are closely linked to pain-processing regions. Regression analysis demonstrated that fALFF values in the occipital lobe in PDN patients were negatively correlated with the IR values but not in the non-PDN group.[58] Nevertheless, the IR correlation still needs further verification due to the small sample size of all these studies.

### *Functional Integration*

Functional integration focuses on the functional connectivity (FC) between different regions to reflect the information transfer and working efficiency of the brain. FC calculates the degree of synchrony of the BOLD time series between brain regions with or without direct anatomic connection. Commonly used computational measurements include seed/ROI-based analysis, FC density, independent component analysis (ICA), and graph analysis. The seed/ROI-based analysis relies on prior assumption and computes the FC of a given region. FC density calculates the correlation between each voxel and all the other voxels in the brain to identify the highly connected functional hubs. ICA is data-drive that separates the BOLD signal into several independent spatial networks that are temporally correlated. Graph analysis, on the other hand, focuses on the brain topology by examining local and global organization properties (Fig. 3).

*HEALTHY SUBJECTS.* In a set of middle-aged healthy adults who were free from depression and diabetes, rs-fMRI data were collected and seed-based FC analysis was performed. The ventral striatum (VS), a central region of regulating depressed mood and sensitive to insulin, was chosen as the seed for FC analysis. Results indicated that higher IR was related to increased connectivity between the VS and anterior mid-cingulate cortex, and the connectivity also predicted depressed mood.[59] This evidence partly explains the associations between diabetes and increased risk of depression, but results were confined to the VS network. Another study on 18 healthy subjects applied both seed-based FC and graph analysis to investigate neural networks both during fasting and postprandial state. Following a meal, the authors found that IR was associated with lower centrality in cingulate cortex, suggesting that insensitivity to insulin may prevent the brain from behavior control and promote overeating and obesity.[60] A similar study using ICA also obtained consistent results, showing that FC of brain networks responsible for food and reward processing was correlated with insulin sensitivity index.[61] Similar to the changes in hippocampal morphology stated in the previous section ([31,34]), deleterious effects of IR on hippocampal connectivity have been observed using ROI-based FC analysis.[62] In this study, ROIs were defined as 10-mm spheres of several regions in default mode network (DMN), and correlations were calculated between these DMN regions and bilateral hippocampal regions. Through comparison between women with high insulin and low insulin ($n = 10$ for each group), the authors found that higher insulin was related to disrupted DMN-hippocampal connectivity and was further correlated to perturbations in performance in executive functioning and global

intelligence.[62] In addition to intranetwork and internetwork connectivity, insulin pathway also modifies the topological characteristics of brain networks. A longitudinal study with an average follow-up of 35 months using the genetic association analyses showed that brain IR pathway, in the absence of diabetes, could modify AD progress by influencing the overall efficiency of brain functional networks.[63] Taken together, these results addressed the influence of insulin on neural connectivity in asymptomatic subjects, and functional integration may be a useful biological marker for cognitive impairment.

*METABOLIC SYNDROME.* In T2DM patients, abnormal functional integration has been widely reported, but its direct correlation with IR was less reported (Table 1). An early study in 2013 assessed FC between the posterior cingulate cortex (PCC), the core hub of cognitive control, and all other regions. T2DM patients, compared with control subjects, showed decreased PCC connectivity that was associated with increased IR, but the association analysis was only performed in five noninsulin-treated patients so that the relationship is still ambiguous.[64] Our group also selected PCC as the seed region to examine its connectivity in 30 T2DM patients. Consistent hypoconnectivity of PCC was observed and negative correlation was found between PCC connectivity and IR, supporting the previous study with a relatively larger sample size.[65] Other methodologies such as ICA, FC density and interhemispheric analysis have all been adopted in T2DM, showing altered connectivity within DMN and between bilateral temporal regions. Impaired insulin sensitivity was correlated with either the altered connectivity with group differences or worse cognitive performance.[66,67]

## Task-State Functional MRI

Performing a task during functional MIR triggers fluctuations in BOLD signals, thus providing the activation pattern in task-related brain regions. Task-fMRI has been widely applied in brain disorders to identify the impaired regions with decreased activation and relate to cognitive impairment (Table 1). N-back task is a continuous-recognition task to measure working memory capacity, requiring participants to judge whether the present stimulus matches the one presented *n* items ago. In a small-sample study with nine healthy older adults, fMRI scan was performed during a two-back working memory task. Results showed that individuals with highest systemic insulin sensitivity were associated with the greatest task-related activation, as well as better performance accuracy.[68] Another study on MetS patients performed a similar two-back working memory task and demonstrated a lower task-related BOLD response in MetS group.[69] Therefore, impaired insulin sensitivity could contribute to worse working memory, probably mediated by the less activation in task-related brain regions. Brain activation during other kinds of tasks were also explored. Compared with lean participants, both obesity and IR were associated with significantly reduced activation throughout the core recollection network (responsible for episodic memory).[28] In systemic IR such as T2DM, reduced activation and impaired deactivation of DMN was observed during encoding and recognition tasks, which were significantly related to IR level.[70] Taken together, task-fMRI studies provided direct evidence of the association between IR and reduced brain activation during task performance, relating both working and episodic memory, and nonmemory tasks.

## Cerebral Perfusion

### Methodological Review

Cerebral blood flow (CBF) is a basic necessity for brain function, as it provides oxygen, energy metabolites and nutrients, and at the same time removes carbon dioxide and cellular waste. It has been suggested that vascular pathology and hypoperfusion contribute to early cognitive impairment,[118] probably through endothelial dysfunction. Therefore, the assessment of CBF is important to detect insidious changes in brain and is potential biomarker of cognitive disorders. Advancement in MRI have allowed direct and noninvasive quantification of CBF through several techniques such as arterial spin labeling (ASL) and phase-contrast MRI technique, none of which requires injection of contrast media or radioactive tracer. In contrast to phase-contrast MRI that only grossly measures total brain perfusion, ASL is more specific that provide regional measurement and location. In addition to CBF, cerebrovascular reactivity (CVR) is more specific to assess endothelial function. It is defined as the change in blood flow in response to increased neuronal activity or a metabolic/vasodilatory stimulus, reflecting the ability of the cerebrovasculature to meet increased metabolic demand.[119] CVR can be assessed as the changes in CBF in response to stimulus, usually the carbon dioxide ($CO_2$) inhalation, at the tissue level using MRI or at the level of a large artery using transcranial Doppler (TCD). These techniques have been widely applied in the clinic to investigate cognitive decline and neuropsychological disorders.

### IR and Cerebral Hypoperfusion

In a study on 120 middle-aged asymptomatic adults, both phase contrast and ASL images were acquired to examine the effect of IR on CBF in macro- and microvessels.[71] The authors demonstrated that subjects with higher IR was associated with lower blood flow within the internal carotid arteries and lower cerebral perfusion in frontal and temporal lobe, indicating that IR affects both micro- and macrovascular flow. Another study directly compared CBF between asymptomatic IR subjects and T2DM patients. Interestingly, the mean cortical CBF in IR subjects were even lower than T2DM patients, which was attributed to the potential beneficial effects of medications treating T2DM.[72] Studies on T2DM patients alone consistently observed diminished regional CBF

across the brain, especially in predilection sites for AD, including the occipital lobe, temporal lobe, thalamus, basal ganglia, cerebellum, and DMN regions[73,74] (Table 1). For example, a 2-year follow-up study assessed the CBF change in T2DM patients using ASL MRI. Patients exhibited decreased global mean CBF as well as regional CBF in the DMN, occipital, and cerebellum networks. Greater decrease in longitudinal CBF values over a 2-year span was associated with higher baseline IR and worse baseline cognitive performance.[73] Our previous study also found decreased regional perfusion in T2DM patients using ASL MRI but showed no change in global mean CBF and cortical volume, indicating that early CBF alterations likely precede volumetric changes.[74] The inconsistencies regarding the global mean CBF could be interpreted that during the earlier stage of cognitive decline, the CBF alterations might be regional rather than global, and the rather gross measurement of global CBF may not reflect the subtle changes.

### IR and Impaired CVR

Several studies have examined reduced CVR in subjects with MetS, but the associations with IR were inconsistent. In a study using TCD,[75] the authors recruited 83 patients with cerebrovascular disease and CVR was calculated as the blood flow increase in response to 5% $CO_2$ inhalation delivered by anesthesia mask. Although the authors demonstrated that the presence of MetS was independently associated with diminished vasomotor reactivity, they failed to show the direct relationship with IR index. A recent study compared CBF perfusion at rest and during mild hypercapnia on ASL MR. Compared with lean subjects, obese participants had significantly lower CVR to hypercapnia, and such impaired CVR was driven by the degree of IR after controlling for BMI.[29] At the present stage, studies evaluating the relationship between IR and CVR are still limited. Given that CVR measurement is a new and evolving technique that varies substantially, the standardization of the acquisition and analytic methods are warranted to understand the pathophysiology underlying IR and cognitive impairment.

## Brain Metabolism

### Methodological Review

Imaging techniques enables the assessment of brain metabolism through the identification and quantification of various metabolites. The most extensively characterized metabolic aspect of the brain is glucose uptake assessed by PET, which reflects energy utilization. Magnetic resonance spectroscopy (MRS), on the other hand, evaluates the spectral peaks associated with tissue metabolites. Identification of altered brain metabolism has been demonstrated to increase the sensitivity and specificity of the clinical diagnosis of AD and is included as a supportive biomarker.[120]

### PET Studies

IR has been associated with hypometabolism that may contribute to cognitive decline, especially in AD-sensitive brain regions. In an FDG-PET study of 150 cognitively normal adults, higher IR was associated with lower total brain and regional glucose metabolism across large portions of the frontal, parietal, temporal, and medial temporal lobes. The association was strongest in the left medial temporal lobe, the hypoperfusion of which in turn was related to worse memory performance.[76] In a small group of 23 healthy adults with newly diagnosed of prediabetes or T2DM, higher IR was associated with an AD-like pattern of reduced FDG uptake in frontal, temporal–parietal and cingulate regions that was independent of age, glucose level and apolipoprotein allele carriage.[77] Interestingly, IR of AD patients was also observed to be correlated with hypometabolism in several brain regions, especially in the medial temporal regions.[78] Notably, temporal regions were addressed in all these studies, suggesting that temporal hypometabolism might be an important link between IR and AD.

In addition to glucose metabolism, other metabolites, especially those linked to AD pathology, have also been

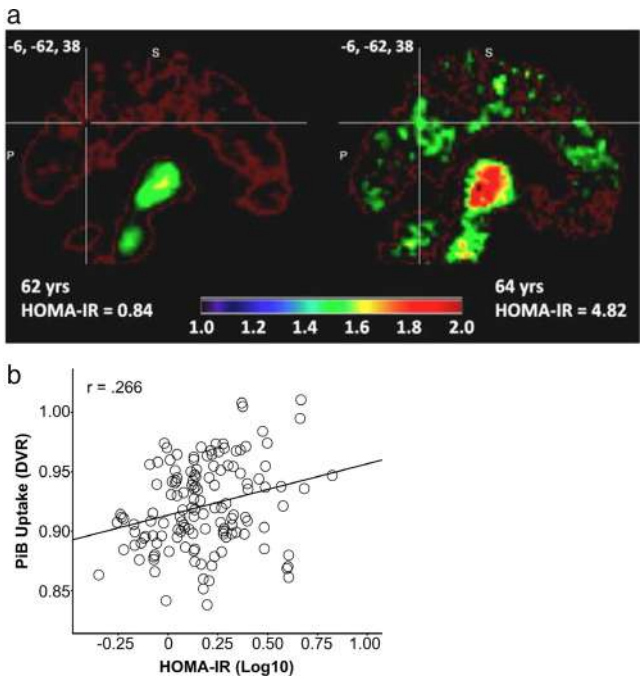


**FIGURE 6: Relationship between insulin resistance and amyloid deposition. (a) Representative images of sagittal Pittsburgh Compound B (PiB) (an indication for amyloid burden) uptake for participants with low IR (HOMA-IR = 0.84) and high IR (HOMA-IR = 4.82). The participant with high IR showed a higher uptake of PiB, as indicated by the color bar of distribution volume ratio. (b) Positive correlation between HOMA-IR and PiB uptake in participants with normal glucose values. Statistics were adjusted for age, sex, apolipoprotein ε4 status, family history of Alzheimer's disease, taking type 2 diabetes medication, body mass index, and the main effects of HOMA-IR and glycemic status. *Source*: Image edited from reference 30 by permission of John Wiley and Sons.**

examined, but results were mixed. One PET study on participants with normoglycemia confirmed a positive correlation between IR level and amyloid deposition, particularly in frontal and temporal areas that are vulnerable to AD[30] (Fig. 6), thus providing direct evidence of early AD pathology. Brain iron overload (BIO) has recently been recognized as an indication for early cognitive impairment in animal and human models. An MRI study assessed BIO using a multiecho gradient-echo sequence and R2* values were calculated to quantify the iron deposition. Through comparison between obese and nonobese subjects, the authors found that IR was independently associated with BIO in caudate and hippocampus, which further correlated with worse cognitive performance.[79] Other studies, on the contrary, found no difference in PET-amyloid load in patients with and without systemic IR, or even an unexpected low amyloid deposition in AD patients coexisting with diabetes[80] (Table 1). Therefore, diabetes-related dementia might indicate different pathophysiological conditions from AD. The recent development of tau-PET imaging has allowed the assessment of brain tau deposition and presents a stronger relation to neurodegeneration than Aβ[121], but there are yet no published results to report on the relation of tau distribution to IR. More advanced imaging techniques for identification of AD pathology and studies with longitudinal design are necessary to unravel the effects of IR on the development of pathological markers of cognitive decline.

### MRS Studies

Using $^{1}$H-MRS, Lee et al. measured prefrontal *N*-acetyl aspartate (NAA) and creatine levels as indications for neuronal viability and energy metabolism in T2DM adults with/without obesity and healthy controls. Results showed that prefrontal NAA levels were lower in T2DM with obesity group, which was correlated with increased IR. IR might therefore be an important link to decreased neuronal viability in the diabetic brain.[81] Myo-inositol (MI) and choline reflect cell damage and myelin damage, respectively. In diabetic patients, increased MI/creatine ratios and choline/creatine ratio have been reported, as summarized in a meta-analysis, highlighting the role of decreased insulin sensitivity in metabolic disturbances.[122] In the above results, although the trend of metabolic changes reflected by MRS were similar to dementia such as AD (i.e., decreased NAA and increased MI and choline), the affected regions were mismatched, which might be attributed to the biased selection of ROIs during MRS data acquirements. More advanced imaging techniques such as whole-brain MRS could help to directly compare the metabolic pattern in IR and dementia patients.

## Treatment Assessment

Given the association between IR and cognitive decline, IR-targeting treatments have been consistently regarded as promising therapeutic strategies to prevent or delay AD development.[10] There are several approaches to treat IR, while the most straightforward one is to increase insulin availability through systemic or intranasal administration. Peripheral administration is commonly used to control diabetes but could cause side effects, such as hypoglycemia and plasma ionic imbalances especially in individuals who do not have diabetes, and might be ineffective due to BBB dysfunction to transport insulin.[10] Intranasal insulin administration, in comparison, relies on the olfactory nerve channels and trigeminal perivascular channels, has been a good alternative to avoid the peripheral side effects. Recent studies have reported various beneficial effects of intranasal insulin, including weight loss, memory and metabolism improvement, both in healthy participants and patients with diabetes and cognitive impairments.[123] Its effects on CNS measurement were also broadly investigated through diverse neuroimaging techniques.

### Intranasal Insulin

In healthy subjects, intranasal insulin administration was proved safe and could induce a significant increase in brain activity in orbitofrontal cortical regions and the hypothalamus, and an increase in CBF in insular cortex and the putamen, as indicated by rs-fMRI and ASL-MRI studies[82–84] (Table 1). These studies had varying sample size, ranging from 17 to 48, but adopted the same dose of intranasal insulin of 40 IU. Imaging measurements were collected before the administration and at several time intervals as long as 120 min, including fALFF from rs-fMRI[82,84] and CBF from ASL sequence.[83] Another study investigated the effects on the neural connectivity under three commonly used doses (40, 100, and 160 IU). A dose-dependent effects of intranasal insulin on the FC of dopaminergic midbrain were observed and the effects varied with pre-existing difference in insulin sensitivity.[85] This study provides important guidance for treatment studies that the administration of intranasal insulin should take dose and insulin sensitivity into consideration to obtain the optimal effects. Apart from the neural activity, intranasal insulin also impacted brain metabolism by increasing energy compounds in healthy subjects, as suggested by $^{31}$P-MRS, which was related to insulin-induced suppression in food intake.[86] According to the study, $^{31}$P-MRS was acquired with a 3D-chemical shift imaging sequence, which was able to detect high-energy phosphate compounds to reflect intracellular energy status. These neuroimaging evidence not only helped localize insulin-sensitive brain regions but also demonstrated the direct impact of intranasal insulin on healthy brain.

The beneficial effects of intranasal insulin delivery on cognitive performance have been repeatedly verified. In a small group of 15 T2DM patients, a single 40-IU dose of intranasal insulin induced acute improvements in visuospatial memory and increased CVR (perfusion change to

hypercapnia on ASL sequence) in attention-related brain regions. Notably, the improved performance and vasoreactivity was correlated, suggesting that intranasal insulin-induced changes in cognitive function might rely on a vasoreactivity mechanisms.[87] Preliminary fMRI studies also evaluated the acute effects of intranasal insulin on 14 T2MD patients, which included enhanced hippocampal connectivity evaluated by ROI-based FC analysis.[88] But further validation is warranted due to the small sample size. In addition, chronic treatment effects have also been evaluated through neuroimaging. In a PET study, a 120-day insulin treatment on MCI or AD subjects induced higher cerebral glucose uptake and preserved functional abilities.[89] In adults with MCI or AD, FLAIR images were segmented through LST toolbox and WMH volume was calculated. 12-month intranasal insulin treatment (20 IU twice daily) significantly reduced WMH volume in deep and frontal regions,[90] supporting the insulin's potential as a therapeutic option for vasculopathy.

### *Other Treatments*

In addition to intranasal administration that usually last for short time, there are other IR-targeting treatment approaches. One MRI study on 11 patients demonstrated that 1-year systemic insulin therapy may have recovering effects on the cortical thinning in T2DM, especially in bilateral middle temporal gyrus and entorhinal cortex.[91] According to an MRS study, 240 minutes of intravenous insulin infusion through euglycemic-hyperinsulinemic clamp could induce an increase in frontal NAA and decrease in frontal and temporal Cho,[92] but only in healthy subjects rather than those with low insulin sensitivity. Such result suggested that the abnormal brain metabolism observed in IR subjects might be caused by the impaired reaction to insulin. The impact of systemic insulin on brain glucose uptake, however, was inconsistent. In experiments relying on FDG-PET measurements, global glucose uptake was found to be stimulated by insulin,[93] but MRS measurements showed that the cerebral glucose metabolism, measured at 5.23 ppm in the occipital cortex and periventricular WM, was an insulin-independent process.[94] Subcutaneous daily administration of liraglutide (a glucagon-like peptide-1 receptor agonist) in AD patients for 26 weeks prevented the decline of brain glucose metabolism but showed no effect on cognition or Aβ burden.[95] Studies are still underway to investigate the neuroprotective effects of IR-targeted treatments to prevent or delay cognitive impairment.

## Conclusions and Future Outlook

IR is associated with alterations in various brain measurements detected by neuroimaging, involving morphology, neural activity, small vessel and WM impairments, brain perfusion, and metabolism. As a promising therapeutic treatment, intranasal insulin also showed improvements in imaging parameters and cognitive performance. However, these results should be interpreted with cautions. First, most of the included imaging studies were cross-sectional and based on a small sample size. This could lead to selection bias and limit the generalization of the results. Second, the reported brain regions that were affected by impaired insulin sensitivity varied across different studies, which might be caused by different population with various ethnicity and health condition. Different imaging modalities, devices and parameters could also contribute to these discrepancies. Future studies based on database with larger sample size, more standardized imaging procedure and processing pipelines should reveal more consistent results. Third, the effects of systemic IR on brain measurements might be confounded or weakened by accompanying risk factors, such as glucose dysregulation, high BMI and waist circumferences, and hypertension. The presence of multiple risk factors might lead to the negative results on the correlation between IR, cerebral alterations and cognitive performance. More diverse populations with follow-up design and strict stratification, including young and middle-aged subjects with and without metabolic disorders, could broaden the understanding of a life-course perspective on how systemic and CNS IR are linked to neurodegeneration.

To summarize, IR was conclusively demonstrated to contribute to cognitive impairment and cerebral abnormalities. Advanced neuroimaging techniques, especially MRI, are useful to detect subtle structural, functional, and metabolic changes that probably precede the clinical symptoms. Brain regions that were commonly reported with alterations include the medial temporal lobe, hippocampus, prefrontal lobe, cingulate cortex, precuneus, occipital lobe and the WM tracts across the globe. Of these, alterations in the temporal lobe are highly reproducible across different imaging modalities. Although the general directionality of the correlations between IR and brain impairments are similar in healthy and MetS subjects (i.e., higher IR associated with more impairments), affected brain regions varied across populations Therefore, the relationship between systemic IR and cognition in the background of metabolic disorders are more complex, probably mediated by disease-specific pathways and multifactorial mechanism. Future studies with coordinates-based meta-analysis might be beneficial to better clarify the IR-related abnormalities in different metabolic background. Taken together, neuroimaging evidence provides us a better understanding of the cerebral alterations in insulin dysregulation, which are important steps for the battle against metabolic and cognitive disorders.

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