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Type 2 Diabetes and Cognitive Impairment: Contributions from Neuroimaging

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Abstract

Type 2 diabetes mellitus (T2D) and Alzheimer's disease (AD) are major public health burdens associated with aging. As the age of the population rapidly increases, a sheer increase in the incidence of these diseases is expected. Research has identified T2D as a risk factor for cognitive impairment and potentially AD, but the neurobiological pathways that are affected are only beginning to be understood. The rapid advances in neuroimaging in the past decade have added significant understanding to how T2D affects brain structure and function and possibly lead to AD. This article provides a review of studies that have utilized structural and functional neuroimaging to identify neural pathways that link T2D to impaired cognitive performance and potentially AD. A primary focus of this article is the potential for neuroimaging to assist in understanding the mechanistic pathways that may provide translational opportunities for clinical intervention.

Type 2 diabetes mellitus (T2D) is a major public health problem believed to affect 25 million Americans, 7 million of whom may be unaware they have the disease. The prevalence of T2D steadily increases with age, with recent estimates suggesting that over 25% of individuals over 65 have the disease¹. Alzheimer's disease (AD) is a brain disorder also linked to aging that affects approximately 5 million Americans. As the population continues to age in the coming decades, it is estimated that the prevalence of AD will triple by the year 2050². Disturbingly, research has begun to link T2D to risk for AD, suggesting that as the population continues to age and incidence and prevalence of T2D increase, this may compound the growing burden of AD on the population. Therefore, it is imperative for research to fully understand the pathways that link these disorders.

Prior to the advent of neuroimaging, identifying alterations in brain structure and function was limited to observations from animal models, autopsy studies, surgical interventions or surface recordings of brain activity. In the past two decades, neuroimaging has given researchers the ability to observe the living brain in a non-invasive way. This review examines how the application of neuroimaging methodologies has led to greater

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understanding of the pathways that link T2D to cognitive impairment and AD. As we develop better understanding of neurobiological alterations that occur in response to the pathophysiology of T2D, these results will provide potential translational opportunities for informing clinical interventions.

Pathophysiology of T2D and AD: evidence for a shared pathway

T2D is a disease of glycemic control, affecting 25 million adults. The prevalence of T2D increases with older age. The main diagnostic criteria for T2D include fasting blood glucose levels greater than 126 mg/dL, HbA1c levels > 6.5%, or glucose levels greater than 200 mg/dL after 2 hours following an oral glucose tolerance test. The hyperglycemia of T2D is caused by two factors: (1) an inability of the beta-cells of the pancreas to maintain normoglycemic conditions in response to increased blood glucose, and (2) a decrease in the ability of insulin to act on cells to promote glucose uptake and suppress glucose production by the liver, a condition termed *insulin resistance*. Obesity, a lack of physical activity, and inflammation all contribute to insulin resistance and promote a pre-diabetic physiological environment. The natural history of T2D is complex, with a variety of genetic, physiological and lifestyle factors contributing to the etiology of the disease³. In addition to older age, a variety of risk factors including sedentary lifestyle, obesity, family history and ethnicity confer increased risk for developing T2D.

AD is a neurodegenerative disorder that accounts for approximately half of reported dementia cases⁴. The incidence of AD increases with older age, increasing from less than 2 (per 100 person years) in individuals under 70 years of age, to possibly more than 6 in individuals 85 years of age or older, although these estimates vary widely across studies⁵. AD displays a characteristic progression of neuronal deterioration, beginning in the limbic regions of the brain – particularly the hippocampus – and spreading throughout the temporal, parietal and frontal lobes^{6,7}. The ability to image these regions using functional and structural neuroimaging has provided critical insights into the progression of disease and attempts to identify imaging biomarkers which may predict progression of the disease and subsequent cognitive decline. The hallmark feature of AD is the presence of extracellular β -amyloid plaques and intracellular neurofibrillary tangles in the brain. Numerous molecular pathways have been identified that could link alterations in insulin signaling, as well as the effects of hyperglycemia, to β -amyloid concentration and tau protein phosphorylation⁸. These pathways include disruption of the Akt and mitogen-activated protein kinase pathways, competitive inhibition of insulin degrading enzyme (which typically degrades β -amyloid), as well as oxidative stress and the formation of advanced glycation end products which result from hyperglycemia⁹. A bi-directional relationship between insulin resistance and pathophysiological markers of AD, such as β -amyloid have been documented¹⁰. Pathology studies on humans have yielded inconsistent results: some studies have found no relationship, or even inverse associations, between T2D and levels of plaques and tangles^{11–13}, but it is possible that the vascular risk factors associated with T2D may lower the threshold at which plaques and tangles impact functioning¹⁴.

Type 2 Diabetes and Cognitive Impairment

Normal aging is associated with decreases in cognitive ability, but prospective studies of those with T2D have shown an increased risk of cognitive impairment and dementia in those with T2D¹⁵. It is unclear whether age and T2D act additively or synergistically to influence the degree of cognitive decline. The relationships between T2D and the rate of cognitive decline have been mixed^{15–17}, but a four year longitudinal study found no evidence for an increase in rate of decline among participants with T2D¹⁸. The relationship between T2D and cognitive impairment has been hypothesized to result from damage that occurs during critical periods of aging, with different risk factors having varying effects on cognition throughout the lifespan¹⁹.

The effects of T2D on cognition are especially pronounced within the domains of memory and executive function. Most studies of the neuropsychological effects of T2D have focused on memory, processing speed and cognitive flexibility. An empirical review of these studies examined cross-sectional and longitudinal effects of T2D on cognition²⁰. Across studies, the most common finding was impairment in processing speed (63% of studies), followed by attention (50%), memory (44%), and cognitive flexibility (38%). Effect sizes were larger in older populations, and the effects generally remained significant after controlling for vascular risk factors.

Identifying the physiological aspects of T2D that contribute to cognitive decline has been an important line of research in hopes of developing preventative interventions. A study of older adults with T2D investigated the relationship between cognition and diabetes disease variables including disease duration, control (measured by HbA1c), insulin therapy, hypertension status, cholesterol levels and polyneuropathy. After controlling for age, gender and education, the only risk factors associated with cognitive impairment were duration and HbA1c levels²¹. These data suggest that disease control and blood sugar level maintenance may potentially confer cognitive benefits, and possibly an additional motivation to encourage patients to engage in achieving blood sugar goals.

Insights from Neuroimaging

The increase in brain imaging studies over the past decade has provided significant insight into understanding how T2D affects brain structure and function, and how these differences – such as hippocampal atrophy and alterations in resting state networks – mirror those seen in AD. A common focus in this decade of research is attempting to identify pathways that may link T2D with cognitive impairment and AD. As computing power and MRI scanner strength have increased, the level of analysis has kept in step, moving from more gross anatomical studies of volume and general atrophy to more fine-grained analysis of white matter tracts, utilizing newer methods such as diffusion tensor imaging. These neuroimaging studies hold the potential to identify early brain abnormalities, both functional and structural that may serve as early biomarkers for later risk of cognitive impairment and the development of AD.

Structural MRI

Volumetric Differences

The majority of studies utilizing neuroimaging to study the effects of T2D on the brain have focused on structural measurements, identifying how whole brain and regional gray and white matter volume relate to the disease. The emerging results have identified a consistent relationship between T2D and cortical and subcortical atrophy, much of which is often focused within the temporal lobes. Initial studies hypothesized that T2D would be associated with abnormalities within the temporal lobe, noting the relationship between T2D and AD²². Utilizing a sample of elderly participants (60–90 years of age), hippocampus and amygdala volumes were compared between individuals with T2D and controls. After controlling for any evidence of vascular disease – including carotid atherosclerosis, white matter lesions and brain infarcts – individuals with T2D had more atrophy of the hippocampus and amygdala. When the degree of insulin resistance was compared to the regional brain volumes, higher insulin resistance was associated with greater atrophy of the amygdala. Later studies using a whole-brain analysis have continued to find a consistent link between diabetes and brain atrophy^{23–25}, and this atrophy is often more pronounced within the hippocampus²⁶. These results demonstrate the capabilities of structural MRI to identify regional brain abnormalities in individuals with T2D that mirror those seen in individuals with cognitive impairment and AD.

Risk Factors

Understanding the components of T2D that contribute to brain atrophy has been an important line of research in order to identify potential points for intervention²⁷. In middle age, glycemic control is an important factor that has been linked to the degree of atrophy. A multivariate regression analysis found HbA1c levels were the only significant predictor of hippocampal atrophy in individuals with T2D²⁶. A later study linked T2D to a reduction in prefrontal and hippocampal volume, and found that obesity (beyond diabetes diagnosis) was a significant predictor of smaller hippocampal volume. The authors hypothesized that inflammation associated with obesity may be the explanatory variable, and future work will be needed to fully characterize the mediators between T2D and changes in brain volume.

An additional factor that could contribute to hippocampal dysfunction and cognitive impairment is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. A study of the relationships between HPA feedback, cognition and brain volume in individuals with T2D found that diminished HPA feedback control was related to decreased cognitive performance²⁸. Separately, obesity was related to decreased hippocampal volumes, and HbA1c predicted prefrontal volumes. These findings suggest that HPA dysregulation may be one pathway linking T2D to decreased cognitive performance, but the brain pathways that mediate these links are not yet understood.

Insulin resistance has recently been shown to be a predictor of gray matter atrophy and cognitive performance²⁹. In otherwise cognitively healthy individuals, insulin resistance was associated with reduced gray matter within the medial temporal lobe, as well as several regions clustered in the frontal, temporal and limbic cortices. A subset of participants

completed a four-year follow up visit to identify if insulin resistance was predictive of cognition and brain volume decline. Insulin resistance at baseline predicted atrophy in several brain regions, including cingulate cortex, hippocampus, parahippocampus and regions in the prefrontal lobe. Insulin resistance was not related to cognitive ability at baseline, but baseline insulin resistance did predict poorer performance on encoding of information at follow-up. This relationship was mediated by progressive atrophy of the hippocampus and parahippocampus. These results highlight the promise of structural neuroimaging to contribute to our understanding of the pathways that link risk factors such as insulin resistance to future cognitive decline.

White Matter Measurements

The hyperglycemia associated with T2D is accompanied by activation of inflammatory pathways, increases in the production of reactive oxygen species and lipotoxicity, culminating in microvascular and macrovascular damage³. As such, it would be expected that individuals with T2D exhibit vascular lesions within the brain that could contribute to the development of cognitive problems. A study of 113 adults with T2D (ages 56–80 years) found a higher number of white matter lesions in the brains of diabetics relative to controls, and this relationship remained after controlling for hypertension³⁰. In addition to higher white matter lesion burden, the diabetic participants performed worse in the cognitive domains of attention/executive functioning, information processing speed, and memory. When neuropsychological performance was compared to structural brain information, deep white matter lesions and silent infarcts predicted information processing speed.

Relationships to Cognition

A recent cross-sectional study investigated the relationship between brain atrophy, lesions and decrements in cognitive function in individuals with T2D³¹. Concurrent with previous research, participants with T2D (n = 350) had more cerebral infarcts and less volume of gray matter, white matter and smaller hippocampal volumes relative to control participants (n = 363). Distribution of gray matter atrophy was particularly localized to temporal, frontal and limbic regions, a pattern characteristic of early AD. Notably, there was no difference in frequency of microbleeds or degree of white matter hyperintensities between groups. Relative to controls, T2D was associated with lower performance on memory and speed of processing measures. In order to investigate the impact of lesions and atrophy on cognition, MRI variables were added in a stepwise regression model after adjusting for demographic characteristics and mood. Addition of gray matter volume reduced the relationship between T2D and cognition by an average of approximately 50%. However, including white matter hyperintensity volume, white matter volume, and infarcts had much smaller effects on the model. These results suggest the atrophy in a pattern similar to that seen in AD may contribute to the cognitive decrements observed in T2D.

Longitudinal studies are beginning to trace changes in cognition and MRI over time in patients with T2D and attempting to identify structural brain changes that may explain the accelerated decline in cognition that is sometimes seen in older adults with T2D. In a four year follow-up study, Reijmer and colleagues³² examined changes in brain volume, white matter hyperintensities, and cognitive functioning between patients with T2D and control

participants. Within the participants with T2D, the authors identified 17 participants (25% of the sample) who were experiencing accelerated decline. Retrospectively, those who had accelerated cognitive decline had larger white matter hyperintensity volumes and larger total brain volume at baseline. At follow-up, those with accelerated cognitive decline had greater increase in ventricular and white matter hyperintensity volume and greater loss of total brain volume, relative to those without accelerated cognitive decline. Although the authors were unable to find an association between clinical risk factors and accelerated cognitive decline, this study was the first to identify volumetric brain parameters that associate with changes in cognition over time.

Longitudinal changes in brain volume were recently linked to changes in cognition in a large study from the Women's Health Initiative³³. Utilizing a large sample of older women (n = 1,366; ages 72–89 years), the authors examined correlations between gray, white and ischemic lesion volumes and cognition. At baseline T2D was associated with smaller gray matter volumes and increased ischemic lesions, replicating earlier studies. There were no cross sectional associations between T2D and white matter volumes. A subset of participants (n = 698) completed a repeat visit approximately five years later. Longitudinally, T2D was associated with an increase in ischemic lesion volumes – but the effects of T2D on loss of total brain volume were non-significant. To identify the effects of brain and ischemic volumes on cognition, all volumes were entered as covariates in a model relating T2D to cognitive performance. Inclusion of brain volumes in the model did not substantially reduce the relationship between T2D and cognitive deficits, suggesting that other factors likely contribute to the impairment of cognition in older women with T2D. These factors could include inflammation, genetic susceptibilities (such as apolipoprotein E), circulating insulin levels, or microstructural abnormalities (discussed below).

Diffusion Tensor Imaging

Diffusion tensor imaging has offered new opportunities to identify microstructural changes in the white matter that accompany T2D and may account for cognitive deficits. In the first study to examine how microstructural white matter changes are altered in T2D, white matter abnormalities (as measured by fractional anisotropy) were identified in the frontal and temporal lobes, but particularly in the temporal stem³⁴. Furthermore, these abnormalities were predictive of immediate memory performance. A larger study on cognitively intact adults with T2D extended these findings by utilizing more imaging parameters including mean diffusivity, transverse diffusivity and fractional anisotropy³⁵. Whole brain analysis found a correlation between disease duration and an increase in mean diffusivity, axial diffusivity and transverse diffusivity. Patients with T2D had a regional decrease in fractional anisotropy in the frontal lobes, primarily due to increased transverse diffusivity. These findings suggest that T2D may be associated with both axonal injury and demyelination, but also illustrate how microstructural techniques will be useful in identifying white matter abnormalities in individuals with T2D. Recent studies have extended these findings of microstructural abnormalities and their relationship to cognitive functioning. Comparison of white matter tracts revealed an increase in mean diffusivity in patients with T2D which, in turn, was related to worse memory performance and slower information processing speed³⁶.

Graph theory³⁷ has provided another method for investigating how the characteristics of white matter networks may relate to cognitive function. In a study of older nondemented adults, those with T2D displayed differences in local and global network properties relative to control participants. Network properties were neither related to memory nor executive functioning, but several network characteristics (clustering coefficient, global efficiency, path length) were predictive of slowed information processing in patients. As these methods become more widely used, neuroimaging will continue to identify structural mechanistic pathways that link T2D to cognitive impairment and AD.

Functional Imaging Studies

While most studies have focused on how T2D relates to structural changes in the brain, a growing literature is documenting functional alterations that occur in conjunction with T2D. Functional studies have included quantification of cerebral blood flow (CBF), glucose metabolism utilizing positron emission tomography (PET), and resting state functional MRI (rs-fMRI). Results from different methodologies have not been as consistent as structural studies, but have begun to identify alterations in brain activity and continued to draw possible links between T2D, cognitive impairment, and AD.

Cerebral Blood Flow

T2D is a major risk factor for cardiovascular disease and vascular dementia. Several studies have attempted to link T2D to alterations in CBF, but with mixed results. Initial studies using single photon emission computed tomography found a reduction in CBF in patients with T2D relative to control participants^{38,39}. Later studies with larger sample sizes have had difficulty identifying consistent patterns of CBF change in individuals with T2D. Experiments by the Utrecht Diabetic Encephalopathy Study investigated associations between T2D and total CBF in a cross-sectional study of 98 patients and 47 control participants. In this sample, total CBF – as measured by blood flow within the internal carotid and basilar arteries – was diminished in patients⁴⁰. However, when the values were corrected for brain volume there was no significant difference in cerebral blood flow between patients and controls. Across all participants, lower CBF was associated with poorer performance on cognitive tests (independent of white matter pathology and infarcts), but this association was independent of diabetes status. Based on these findings, the authors concluded that total CBF was likely not the underlying cause of cognitive impairment in patients, but it was unclear if cerebrovascular reactivity was a contributing factor.

To address both the question of reactivity and longitudinal effects of CBF on changes in cognitive function and brain volume, a four-year follow up study was conducted⁴¹. Cerebrovascular reactivity was measured by observing the change in blood flow in response to an inhaled carbon dioxide mixture. At baseline, there was no relationship between cerebrovascular reactivity, cognition, and brain volume or white matter disease. At follow up, cognition had declined at similar rates for patients and controls⁴², but in patients with T2D this decline was not predicted by cerebrovascular reactivity or CBF. Similarly, CBF and cerebrovascular reactivity at baseline did not predict changes in brain volume. The authors concluded that these vascular measures may not play a causative role in cognitive decline and atrophy in T2D, but other vascular brain damage may still play a role in these

factors. Additionally, measurement of CBF using flow through arteries that feed the brain provides only a gross measurement of total blood intake, without reference to regional differences that may increase or decrease with disease pathology.

PET Imaging

The question of longitudinal regional changes in CBF was addressed recently by the Baltimore Longitudinal Study of Aging utilizing ^{15}O -water PET imaging⁴³. The initial study aimed to identify how cardiovascular risk (measured using the Framingham Heart Study score) related to longitudinal changes in regional CBF. Participants included 97 older adults (mean baseline age: 69.5 years) with varying levels of cardiovascular risk and free of cognitive impairment. Participants completed PET scans annually for up to eight years and changes in CBF were modeled using cardiovascular risk score as the independent predictor. Higher baseline levels of cardiovascular risk were associated with decreases in CBF in several brain regions, independent of changes in tissue volume. Within the areas that displayed decreases, relationships were examined for individual risk factors that comprised the cardiovascular risk score. T2D had an independent relationship with CBF declines in one region, insular cortex, and this relationship was not attenuated after controlling for changes in brain volume. One limitation of this study was that it included only 19 participants with T2D (total sample = 97 participants), and thus may have been underpowered to detect changes in other brain regions. These results suggest that longitudinal CBF changes that accompany T2D may be regionally specific, but subsequent studies need to include larger samples that are specifically designed to test for these differences.

A second study by the Baltimore group examined how impaired glucose tolerance in midlife (mean age = 57 at baseline) predicted subsequent changes in CBF, again measured by ^{15}O -water PET imaging⁴⁴. Participants (n = 64, free of T2D) completed oral glucose tolerance tests and were divided into those with impaired glucose tolerance (n = 15) and normal glucose tolerance (n = 49). Longitudinal changes in CBF were then compared between groups. Glucose tolerance status was associated with longitudinal increases and decreases in CBF in several regions. Relative to participants with normal glucose tolerance, those with impaired glucose tolerance had greater CBF decreases in regions including orbitofrontal cortex, superior temporal gyrus and the inferior parietal lobule. Greater increases in CBF were seen in regions including inferior frontal gyrus, midtemporal gyrus, and globus pallidus. Accounting for apolipoprotein-E status did not affect the results, but controlling for body mass index eliminated orbitofrontal and inferior parietal lobule relationships. However, all associations between glucose tolerance and increases in CBF remained significant after covarying for body mass index. These results suggest that impairments in glucose tolerance – an early marker for diabetes risk – may hold predictive value for subsequent changes in CBF in numerous brain regions. Participants in this study were free of T2D, and thus free of insulin treatment and diabetes intervention. However, as a subclinical sample, the longitudinal changes in CBF may continue to change if those with impaired glucose tolerance progress to T2D.

Alterations in cerebral glucose metabolism that accompany prediabetes and T2D have been investigated in a cross sectional study utilizing ^{18}F FDG PET⁴⁵. Insulin resistance was

estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), and participants included older adults (mean age = 74) with pre-diabetes (n = 11), T2D (n = 12) or normal glucose tolerance (n = 6). At rest, in participants with prediabetes or T2D, higher insulin resistance was associated with reductions in glucose metabolism in regions including posterior cingulate cortex, precuneus, temporal lobes and regions of prefrontal cortex. In adults with normal glucose tolerance, there were no associations between insulin resistance and regional cerebral glucose metabolism. A separate scan was conducted as participants completed a memory-encoding task. Healthy participants displayed the predicted increase in activation in regions associated with memory encoding, including medial cingulate, frontal and temporal cortices. Qualitatively, those participants with prediabetes/T2D had a more widespread pattern of activation extending into putamen, cerebellum and thalamic regions. Within that group, memory recall scores were associated with increased metabolism in regions including the posterior cingulate and left frontal and temporal cortex. Based on this pattern of diffuse activation, the authors draw parallels to changes in cerebral metabolism that are commonly seen in AD.

Resting State Functional MRI

Measuring activity of the brain using rs-fMRI has had a major impact on identifying functional networks that are spontaneously active in the brain in the absence of a task or external stimulation⁴⁶. As the properties of these networks have become better understood, research has begun to identify alterations in resting state networks that co-occur with numerous disorders. Most research has focused on schizophrenia, AD and depression⁴⁷, but a growing body of research has identified alterations in resting state networks that accompany T2D. One of the first studies to utilize rs-fMRI in individuals with T2D used a region of interest approach to identify how connections between brain regions were altered in conjunction with T2D in elderly participants⁴⁸. Resting state signal was extracted from bilateral hippocampus regions and correlated with activity across the brain. These network maps were then compared between patients with T2D (n = 21) and controls (n = 19). Patients with T2D had reduced functional connectivity between the hippocampus and numerous regions that are typically associated with the “default mode network,” including the anterior cingulate cortex, inferior parietal and medial temporal lobes. Participants also completed neuropsychological tests that revealed differences in memory and executive function domains in participants with T2D, but the study did not examine direct associations between differences in cognition and brain activity.

Alterations in default mode network connectivity were recently examined in middle age adults (45–66 years old) including 10 patients with T2D and 11 age-matched controls⁴⁹. Patients exhibited lower connectivity between the posterior cingulate and several default mode regions, including middle temporal, medial frontal and inferior frontal gyri. In this sample, no between-group differences were found in hippocampus volume or cognitive performance, and neither hippocampus volume nor cognitive scores correlated with functional connectivity measurements. However, due to the small sample size, these null findings could be the result of low statistical power.

Resting state regional differences in activity were recently investigated using amplitude of low-frequency fluctuations, a separate method for identifying rs-fMRI components⁵⁰. The study extended the findings of alterations in the temporal lobe, finding reduced amplitude values in bilateral middle temporal gyrus as well as several other regions. Activity in the middle temporal gyrus was inversely correlated with HbA1c and executive functioning. These results continue to indicate that T2D not only affects structure of the temporal lobe, but these alterations in structure may be accompanied by functional alterations. Furthermore, these findings reinforce the importance of HbA1c as a significant predictor of brain volume, adding to the literature that identifies glucose control as an important factor in understanding decline.

Although the literature linking T2D and alterations in brain activity has been limited relative to the size of the structural imaging literature, it has contributed to models that link T2D and its risk factors to regional changes that mirror those seen in cognitive impairment and AD. Several of the functional imaging studies are limited by small sample sizes, and lack of prospective design. However, the findings continue to link alterations within temporal and limbic structures to the cognitive dysfunction that accompanies T2D. Future studies employing prospective designs and accounting for more of the physiological components of T2D have the potential to identify early functional alterations that may serve as independent predictors for risk of future cognitive decline. Combining functional and structural methodologies will continue to inform models for the pathophysiology that links T2D and its risk factors to cognitive impairment.

T2D and AD Biomarkers

Interactions Between T2D and AD Progression

As the population becomes older and the incidence of T2D and AD increases, it is critical to identify pathways within the diseases that may interact, possibly leading to worse outcomes. To date, only a few pioneering neuroimaging studies have included groups of patients with comorbid T2D and AD to identify the interactions between the diseases. An initial study measured the degree of cortical atrophy in patients with comorbid T2D and AD relative to AD patients without T2D⁵¹. Despite equal performance on neuropsychological function, participants with comorbid T2D and AD had significantly more cortical atrophy relative to those patients without T2D. This effect remained significant independent of age, hypertension, history of vascular intervention, or infarcts. There was a non-significant trend toward more infarcts in patients with both disorders, leading the authors to conclude that a “dual pathology” – both an increase in atrophy and infarcts – may account for the increase in dementia risk in participants with T2D. These results highlight the potential additive effects of T2D and AD on neurobiological pathways that contribute to cognitive impairment, as well as the danger of an increasing prevalence of both diseases.

β-amyloid Imaging

How insulin resistance relates to β-amyloid burden in brain tissue was recently investigated in the Baltimore Longitudinal Study of Aging cohort⁵². The study included both autopsy samples (n = 197) and in vivo imaging of β-amyloid in living participants (n = 53). Presence

of β -amyloid was assessed using Pittsburgh Compound B (^{11}C -PiB), a radiotracer utilized in PET imaging to identify plaques. Insulin resistance was quantified by oral glucose tolerance testing performed annually since entry into the study. Within the autopsy samples, there was no relationship between glucose, insulin and insulin resistance (as measured by HOMA-IR) and AD pathology. These null results maintained across different analytic strategies (categorical/continuous) and with various characteristics of the oral glucose tolerance test (rates of change, mean glucose levels at 120 minutes, etc.) When the sample was split based on dementia status (101 with dementia, 96 without), there were no intergroup differences in fasting glucose, insulin, or insulin resistance values. Similarly, there were no differences in AD pathology across groups based on the use of glucose-lowering drugs or insulin use.

Similar results were found using ^{11}C -PiB imaging: there were no group differences in ^{11}C -PiB retention when participants were split by glucose response, fasting insulin, or insulin resistance values. Participants in the top one-third of ^{11}C -PiB deposition had no difference in glucose or insulin scores relative to those in the bottom third of ^{11}C -PiB deposition. A region-of-interest analysis of the posterior cingulate/precuneus and medial temporal lobe also failed to find any differences in ^{11}C -PiB deposition. The authors note several shortcomings of the study, including that ^{11}C -PiB selectively marks β -amyloid burden, but provides no measurement of protein aggregation other than β -amyloid. Second, pathological methods included silver staining rather than immunostaining, which is more sensitive to detecting plaques. Additionally, the study did not account for differences in vascular damage nor did it account for apolipoprotein-E allele status. In summary, prospective measurements of glucose homeostasis and insulin resistance showed no associations with postmortem autopsy measures of AD pathology, or with in vivo measurements of β -amyloid deposition using ^{11}C -PiB.

Neuroimaging can continue to provide useful insights into the mechanisms between T2D and AD pathology, even though the initial studies have had mixed results. Future studies including participants who have a longer history or higher severity of T2D may provide additional insights into how these factors contribute to AD pathology. The recent development of additional markers of β -amyloid, such as Florbetapir (^{18}F) that has a longer half-life than ^{11}C -PiB, may provide more sensitive imaging measures of β -amyloid deposition.

Administration of Insulin and Oral Agents

Insulin has been shown to have beneficial effects on memory and cognition^{53,54}. AD is associated with alterations in insulin concentrations and insulin sensitivity within the brain and cerebrospinal fluid⁵⁵. Studies in rodent models have suggested that insulin signaling contributes to optimal hippocampal function⁵⁶, and therefore restoring insulin levels to normal could provide a therapeutic opportunity for individuals with AD. An initial trial that administered intranasal insulin for three weeks to patients with AD and amnesic mild cognitive impairment found improvements in delayed story recall⁵⁷. Following up on these results, a pilot clinical trial was conducted to identify the effects of longer-term intranasal insulin administration on cognition, brain function and cerebrospinal-fluid markers of AD⁵⁸. Participants with amnesic mild cognitive impairment or probable AD were assigned to one

of three conditions – 20 IU of insulin, 40 IU of insulin, or placebo – administered daily for four months. At the end of the trial, subgroups of each condition completed lumbar punctures to measure β -amyloid and tau levels in CSF, or PET scans to quantify cerebral metabolic rate. Insulin administration relative to placebo had protective benefits on cognition (less decline relative to placebo) and the 20 IU dosage was associated with better memory performance relative to both 40 IU and placebo. Insulin treatment did not have significant effects on β -amyloid or tau levels in CSF, but did affect cerebral metabolism. Over the four-month period, participants receiving placebo experienced a significant decline in metabolism, but participants who received intranasal insulin displayed no change in cerebral metabolism during the same time period. These results suggest that administration of insulin into the central nervous system via the nasal passage may have protective effects on cognition accompanied by altered progression of brain function. Future studies will be needed to fully understand what underlies the protective effects of insulin on brain function, and how long these effects may persist with continued intervention.

Numerous oral agents are available to target the pathology of T2D, with added convenience relative to intranasal administration, but the cognitive effects of these medications vary. Neuroimaging studies of the structural and functional effects of oral agents as they relate to AD pathology will be an important future direction. Several studies have hypothesized that targeting insulin resistance could hold potential for preventing cognitive decline and AD⁵⁹. Initial data suggested that the insulin sensitizer Rosiglitazone may improve cognition in mild to moderate AD⁶⁰, but a placebo-controlled phase III trial failed to find any evidence of benefits in cognition or global function⁶¹. Metformin use has been associated with reduced risk of dementia⁶², but long term use was linked to an increased risk of AD⁶³, and another recent study observed poorer cognitive performance among patients who were using metformin⁶⁴. Incretin hormone receptor agonists, particularly GLP-1 analogues, are a promising class of drugs that can cross the blood brain barrier⁶⁵ and have been shown to have beneficial effects in learning and AD pathology within murine models^{66,67}. The effects of GLP-1 agonists on human cognition are currently unknown, but a clinical trial was recently completed (NCT01469351) that examined the effects of a 6-month treatment of liraglutide on β -amyloid deposition, as measured by ¹¹C-PiB in patients with AD.

Conclusion

Over the past decade as we have struggled with increasing rates of T2D, neuroimaging has served as a critical tool for beginning to identify alterations in brain structure and function that may link T2D to AD. Volumetric studies have identified the impact of T2D on brain volume, and more powerful research scanners have begun to identify microstructural white matter abnormalities that will assist in understanding cognitive impairments that accompany T2D. Novel ligands such as ¹¹C -PiB now allow observation of β -amyloid in living tissue. Network analysis of brain activity is identifying functional brain networks that will illuminate how T2D affects activity across brain regions, which in turn contribute to cognitive dysfunction.

The coming decade will continue to build on these methods and findings, hopefully identifying interventions and strategies to slow or reverse cognitive and neurological

dysfunction. Currently a limited number of studies have utilized more advanced neuroimaging computational methods, such as graph theory, to more fully characterize patterns of change. Identifying how patterns of connectivity and activity change longitudinally, as well as in response to treatment, may provide critical insights into identifying biomarkers that can translate into clinical practice. No studies have yet implemented methodologies such as machine learning to identify alterations in activation patterns that may occur in T2D and serve as early markers of future cognitive impairment. Fortunately, a significant body of research has emerged utilizing these methods for early detection and potential clinical use of neuroimaging in AD. In the coming decade, as prevalence of T2D continues to increase and the population continues to age, it will be imperative to extend these methods to understand how T2D, cognitive impairment, age and AD interact. Neuroimaging promises to extend our understanding of the mechanisms that link these factors, and holds the potential to provide translational opportunities for intervention.

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