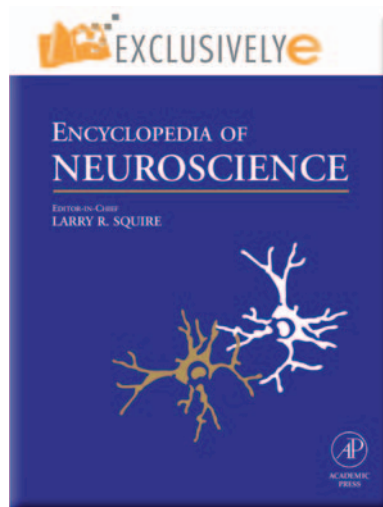


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## Diabetes Type 2 and Stress: Impact on Memory and the Hippocampus

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### Introduction

The aim of this article is to present our understanding of how the abnormalities in peripheral glucose control and elevations in cortisol levels associated with type 2 diabetes mellitus (T2DM) may give rise to medial temporal lobe (MTL) pathology and dysfunction. The article falls into four main sections: Memory and aging, effects of glucocorticoid functioning on the brain, impact of diabetes on the brain, and, finally, an integrative model that attempts to explain how the specific MTL dysfunction may come about. First, we give a brief introduction on normal and pathological changes in the aging brain before we explain how hypothalamic–pituitary–adrenal (HPA) axis functioning, that is, cortisol secretion and control, can affect brain and cognition. Next, we summarize evidence that insulin resistance and type 2 diabetes can contribute to a reduced integrity of the MTL memory system. In this context we highlight the multiple interactions between the glucoregulatory system and the neuroendocrine stress system. The last section presents an explanatory model of how we conceptualize the above-mentioned processes give rise to the MTL impairments, and provides a framework for the generation of specific hypotheses for future research in this area.

### Memory in Aging: Normal Changes, Mild Cognitive Impairment, and Dementia

Cross-sectional studies of human aging have consistently reported that, relative to younger individuals, normal elderly show performance reductions in memory, attention, visual–spatial function, abstraction, and problem solving. Longitudinal studies provide a refinement by demonstrating that over time the most salient declines are in tests sensitive to frontal lobe function, namely working memory (requiring the short-term storage and manipulation of information prior to responding), psychomotor efficiency, word knowledge, attention, learning, and problem solving. Although the majority of this literature suggests that most cognitive deficits are related to frontal dysfunction, some research suggests that MTL, which

includes structures such as the hippocampus, amygdala, and entorhinal cortex, may also be involved. In normal aging cognitive deficits do not generally result in impairments in everyday functioning.

Memory impairments have been recognized for many years as the most reliable early clinical symptom in dementia of the Alzheimer's type, and both the pathology – namely the distribution of neurofibrillary tangles (one of the two types of brain pathology that are necessary for a brain diagnosis of Alzheimer's disease (AD)) – and the *in vivo* imaging literature indicate that the earliest lesions are in the MTL. In addition, among elderly individuals who demonstrate subtle impairments in functioning and who may be considered at higher risk for significant cognitive decline and AD, those who have so-called mild cognitive impairment (MCI), demonstrate predominantly MTL pathology in the earliest stages of cognitive deterioration. With that being said, most middle age and elderly individuals who present with memory and other cognitive impairments, but with no impairments in overall functioning, will not go on to develop dementia.

### Links between Diabetes and Dementia

There is evidence from longitudinal population-based studies that the risk of dementia is higher among individuals with diabetes than among those without it. The risk seems to be higher for individuals with the Apo E  $\epsilon$  4 genotype or receiving insulin treatment. The Apo E gene, which has a polymorphic distribution in the population, codes for a protein that is important in lipid transport and metabolism. Individuals with one or two copies of the Apo E  $\epsilon$  4 allele have a higher risk for cardiovascular disease. However, findings have been inconsistent as to whether this increased risk is specific for AD, multi-infarct dementia (MID), or dementia in general. Although the associations between diabetes and dementia are intriguing, none of these studies has directly assessed the impact of T2DM-related factors. For example, the impacts of hypertension and cardiovascular disease, conditions associated with T2DM, cognitive decline, and dementia, have not been evaluated. Although diabetes is often associated with vascular pathology ranging from micro-vessel disease to hypertension and stroke, studies to date have not provided sufficiently detailed data on those diabetes-associated factors to better ascertain how they may mediate or modulate the risk for dementia associated with diabetes.

The magnitude of the risk for AD related to diabetes is only modest and smaller than that of some nonspecific risk factors, such as low education or history of head trauma. It is possible that the impact of diabetes, analogous to that of low education and head trauma, is to reduce the brain reserve of affected individuals, and thus the associations observed between diabetes and AD may also be nonspecific. This position is supported by the extant pathology literature. Out of the autopsy series available, most fail to find increased Alzheimer's pathology in those individuals with diabetes (with some studies actually finding reduced AD pathology among diabetics), and only one series found a nonsignificant increase among Apo E  $\epsilon$  4 diabetics. However, based on indirect evidence some investigators have speculated that diabetes may be 'mechanistically' linked to AD. This hypothesis is based on observations that insulin acutely enhances memory in healthy older subjects, but is less able to do so in AD patients. In addition, insulin might increase levels of inflammatory cytokines and amyloid beta in the brain. Future research will test these hypotheses.

### **The Impact of Cortisol on Cognition and the Brain**

Stress is conceptualized as a perceived challenge to the organism's balance or homeostasis, and the resulting processes intended to return the organism to equilibrium are termed 'allostasis.' The most prominent of these processes is the activation of the HPA axis. This activation results in the release of glucocorticoids (GCs) and the activation of the sympathetic nervous system (SNS), leading to the release of catecholamines (epinephrine and norepinephrine). In the presence of an acute stress these responses protect and allow the organism to adapt to its changed internal or external environment. However, when the stress becomes chronic or the organism responds inappropriately (e.g., poor habituation or a failure of negative feedback), multiple systems, including the brain, are negatively impacted. This state has been called 'allostatic load.'

GCs, depending on their timing, can have positive or negative acute effects on memory. For example, stress (or an acute increase in GCs) during learning, or immediately thereafter, leads to enhanced memory consolidation. In contrast, an equivalent rise in GCs shortly before delayed retrieval causes impaired retrieval. Animal and human studies suggest that both the positive and negative GC effects are mediated by interactions between amygdala and hippocampus, two limbic structures central in emotional processing and memory formation.

Chronic stress leads to negative consequences in both animals and humans. In animals, chronic stress causes structural alterations of neurons (dendritic atrophy or dendritic remodeling) in hippocampus and prefrontal regions. In addition, stress negatively impacts neurogenesis and alters cholinergic, serotonergic, and dopaminergic systems. These changes are associated with impaired memory performance, although the mediating mechanisms remain unclear. For example, both rats and tree shrews subjected to repeated stress develop impairments in hippocampal-based memory tasks. In contrast, amygdala-mediated tasks, such as fear conditioning, are enhanced. Age affects the organism's response to stress. Although there is large individual variability, aged individuals have increased GC levels as well as impairments in HPA axis negative feedback, both of which have been associated with cognitive impairments. For example, rodents with age-associated increases in HPA activity had impairments in memory performance, whereas those with normal levels did not. Moreover, pharmacological or behavioral interventions that stabilized HPA activity throughout life offered protection from those age-associated memory problems.

In the human, conditions leading to substantially elevated cortisol levels are characterized by impairments in memory, attention, and mood. For example, the hypercortisolemia present in Cushing's disease is associated with reductions in memory performance and hippocampal atrophy, deficits that are at least partly reversible upon successful reduction of the supraphysiological cortisol levels. Elevations in basal GC levels within the normal range have also been associated with cognitive dysfunction; older individuals with higher cortisol levels show poorer memory and faster cognitive decline. However, the causal order of these associations remains unsettled. The behavioral impairments may be secondary to cortisol-induced hippocampal atrophy. However, given the importance of the hippocampus on cortisol feedback inhibition, the cortisol elevations may be the result rather than the cause of hippocampal atrophy. Nevertheless, some recent studies offer indirect support for primacy of cortisol elevations leading to hippocampal damage. For example, self-reported stress proneness is associated with an increased risk for dementia, a disease that involves hippocampus and other MTL structures in its initial stages. Further indirect support is offered by the finding that individuals with genetically determined increases in tissue GC bioavailability have a higher risk for AD.

HPA axis dysregulation, in addition to possible direct effects on the hippocampus, may affect memory through its impact on other related systems also known to affect memory. For example, GCs can

impair insulin sensitivity or lead to enhanced visceral fat deposition and altered food intake, which in turn can lead to problems with glucose control, conditions known to be associated with reductions in memory performance. Interestingly, the adverse consequences of stress on the hippocampus occur faster in diabetic animals, suggesting an increased vulnerability of the diabetic brain. The interactions between the HPA axis and the glucoregulatory system will be illustrated in the following section.

### **Interactions between Cortisol, Insulin Function, and Type 2 Diabetes**

Research conducted during the past decade has demonstrated that the HPA axis and the glucoregulatory system interact at multiple levels. Examples can be found for interactions at the behavioral and system level as well as on particular aspects of neuronal or transporter functioning.

Cortisol secretion and peripheral glucose regulation are closely linked. For example, we know that physiologically increased cortisol acutely inhibits insulin release, and that pharmacological doses of GCs cause reductions in glucose disposal (insulin resistance). In addition, in animal models GCs reduce the amount of insulin transported across the blood-brain barrier (BBB), and in large doses inhibit neuronal and glial glucose uptake in the hippocampus but not in other brain regions (e.g., hypothalamus, cerebellum, or cortex). Similar effects have been noted in the human; we have shown that acute cortisol administration leads to a specific *in vivo* hippocampal reduction in glucose utilization as seen with positron emission tomography. It is noteworthy that the hippocampus is the brain area with greatest co-localization of cortisol and insulin receptors. It is possible that the GC-mediated reductions in memory performance are due to their impact on hippocampal energy status.

Chronic stress in animals leads to effects at a behavioral level. Investigators have documented that chronic stress, through a facilitating effect on the HPA axis, leads to changes in eating habits. These animals seek more 'comfort' food and the GC elevations promote visceral fat deposition. In the human, chronic stress, with the associated hyperactivity of the SNS and HPA systems, can lead to the metabolic syndrome, which is characterized by central obesity, impairments in glucose regulation, hypertension, and abnormal lipid profiles.

Problems with peripheral glucose control may potentiate the deleterious effects that cortisol exerts on the brain. For example, when diabetic rats are stressed, they develop extensive hippocampal damage in one-third the time it takes nondiabetic animals

to develop equivalent stress-mediated damage. It has also been shown that diabetic rats have chronic elevations of basal GCs and have greater and more prolonged responses to stress. We also know that reduced hippocampal integrity may lead to impaired cortisol feedback inhibition, and thus to elevated cortisol secretion. Adding support to the notion that the stress and the glucoregulatory systems interact in their influence of cognition during aging are observations from the MacArthur Study on Successful Aging. These investigators reported that summary measures of allostatic load, consisting of a combination of stress hormone measures and metabolic syndrome measures, were a superior predictor of cognitive and functional decline in older individuals.

Although it is difficult to ascertain cause and effect, it may be that abnormal glucose tolerance causes hippocampal dysfunction, which then affects cortisol feedback control, which in turn may result in elevated cortisol levels, thus contributing to a vicious cycle of further hippocampal damage.

### **Impact of Diabetes on the Brain**

Neurons neither synthesize nor store glucose and are hence dependent on external sources to meet their energy demands. For a long time it was thought that the brain sat in a privileged position and that its glucose supply was independent of what was happening in the periphery. Only in recent years has this view changed, and it has become apparent that glucose transport into the brain is affected by the peripheral environment and that insulin, insulin receptors, and insulin-sensitive glucose transporters (GLUTs) are all present in brain, although their function remains unclear.

Under normal physiological circumstances the metabolism of glucose borne by the blood accounts for 99% of the brain energy needs. Although glia and astrocytes contain glycogen, the contributions of this glycogen to the overall energy demands of the brain are not known. (Note: It is our opinion that understanding the role of glycogen in brain will be an area of great interest in the near future. This opinion is based on the fact that upon restoration of euglycemia after an episode of hypoglycemia, glycogen deposition in brain goes up markedly, perhaps protecting the brain from subsequent hypoglycemic episodes. In addition, experimental animals subjected to weekly episodes of significant hypoglycemia perform better than sham animals on memory tests during euglycemia, and this improved memory performance is preserved in these animals in old age. Whether these memory-enhancing and protective effects are due to hypoglycemia-based improved transport of glucose

across the BBB or to increased deposition of brain glycogen, or both, has yet to be established.)

Despite the fact that the brain depends on peripheral glucose, up until 10 years or so ago, it was commonly believed that the brain was able to obtain all the metabolic substrate it needed, irrespective of what was happening in the periphery. Although the transport of glucose across the BBB remains poorly understood, we now know that the peripheral environment can exert significant influences on BBB transport. For example, the BBB glucose transporter can be up- or downregulated, dependent on the sustained peripheral glucose levels. Additional potential links between systemic and brain glucose control and metabolism are offered by the presence of insulin and insulin-sensitive glucose transporters (GLUT4) in the brain. In peripheral tissues insulin regulates glucose homeostasis through effects on GLUT4, the glucose transporter highly expressed in fat and muscle. GLUT4 is also expressed in brain, including the hippocampus. However, it is not known if insulin affects glucose uptake into the hippocampus. Moreover, it remains to be seen how brain GLUT4 behaves in a state of peripheral insulin resistance. Regardless, it is clear that glucose uptake and utilization in the brain are complex and that their regulation is yet to be understood.

Because impaired insulin function (or absence of sufficient insulin) and the resulting hyperglycemia are at the core of diabetes, it is likely that these fluctuations will have an impact on the brain and its functioning. There is mounting evidence that diabetes, whether it is type 1 or type 2, has a negative impact on both cognition and brain. However, the resultant adverse effects may vary by the type of diabetes. A straightforward assessment of the differential impact of type 1 and type 2 diabetes on cognition and brain is complicated by the fact that most studies only contrast one type of diabetic patient against controls and do not control for comorbid conditions or possible mediating factors such as hypertension, vascular disease, and depression, which are often associated with diabetes.

Adults with type 1 diabetes mellitus (T1DM), when contrasted to nondiabetic controls, show reduced performance on several cognitive domains, including psychomotor efficiency, intelligence, visual and sustained attention, and speed of information processing. The majority of studies of adults with T1DM demonstrate that the presence of macrovascular disease, but not glycemic control or the number of hypoglycemic episodes, contributed to the lower cognitive performance described. Cognitive deficits are also observed in children and adolescents with T1DM, but there's no consensus in the literature as to whether age of onset or

disease duration affects the severity of those cognitive deficits. Furthermore, it remains unclear whether the cognitive impairments worsen with age. In addition, the nature of the impact on cognitive functioning of episodes of either hypoglycemia or hyperglycemia remains unclear. Different studies have evaluated study participants of various ages and have used different test batteries, which do not permit a straightforward comparison across studies.

In contrast to the findings in T1DM, studies of T2DM show mostly impairments in verbal memory and processing speed, whereas other cognitive domains, such as visuospatial function and attention, remain preserved. There is also evidence that in T2DM, glycemic control might influence the cognitive deficits; improvements in glucose control by either pharmacological or behavioral interventions have been associated with attenuation of the cognitive deficits. Additionally, cognitive deficits seem to be augmented by factors associated with T2DM, such as hypertension, depression, and vascular disease. Some studies suggest that severe memory impairments are only seen in older T2DM populations and that the cognitive deficits seen in T2DM represent an acceleration of normal brain aging.

There are only a few *in-vivo* imaging studies in diabetes, and existent studies have not contrasted T1DM and T2DM. The overall findings are that type 1 diabetes leads to general brain atrophy, whereas T2DM seems to preferentially involve MTL structures, and that these findings may be independent of vascular complications. In our own work we have demonstrated that among relatively young individuals with well-controlled T2DM, only reductions in memory, performance, and hippocampal volume separate them from age-, gender-, and education-matched normal controls. In addition, we have described very similar cognitive and imaging findings among normal middle-aged and elderly nondiabetic individuals with impairments in glucose tolerance. Few studies evaluate the brain in T1DM, and there is only one study of adults with T1DM that looked at both cognition and brain with magnetic resonance imaging (MRI). One small pilot study in adults with longstanding T1DM observed reductions in psychomotor speed and selective attention which was accompanied by global cerebral atrophy (increase in cerebrospinal fluid and decrease in total brain volume). However, no evidence for hippocampal volume reductions and memory impairments were detected.

In recent years, paralleling the obesity epidemic, the prevalence of T2DM within the population has risen even among children and adolescents. To date there are no reports in the literature evaluating cognition and brain status among children with



T2DM. Preliminary pilot data from our group shows widespread cognitive impairments among obese adolescents with T2DM when contrasted with age-, gender-, and education-matched obese controls.

The precise mechanisms by which diabetes and impaired glucose regulation affect memory are not clear, but the risk factors that are often associated with insulin resistance and that are part of the metabolic syndrome, namely hypertension and dyslipidemia, might play a role. In the next section we outline a model of how diabetes directly affects brain structures that are central for memory process, that is, the hippocampus.

### Possible Mechanisms for the Cognitive Impairments Seen in T2DM

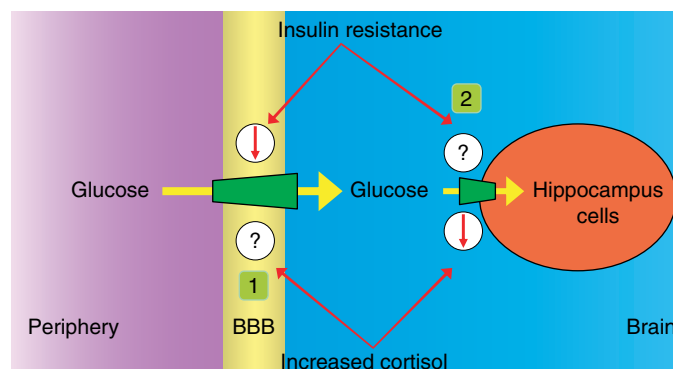
Glucose is transported across the BBB by GLUT1, a glucose transporter highly expressed in the vascular endothelial cells of the BBB. Although the regulation of glucose transport into the brain is not well understood, GLUT1 has very high affinity for glucose and is saturated at normal blood glucose levels. Previous work in animal models has established that long-term elevations in peripheral glucose result in decreased transport of glucose across the BBB, whereas the opposite is true for chronic hypoglycemia, in which there is an increase in transport across the BBB. In both these circumstances it is believed that the amount of GLUT1 expressed at the BBB is responsible for the changes in glucose transport.

During brain activation, there are measurable shifts in the local concentrations of available glucose. For example, visual stimulation reduces visual cortex glucose concentrations as seen with MRI-based spectroscopy. Brain glucose levels can be measured directly with microdialysis probes in free-moving rats. Using

these techniques there is evidence that glucose is compartmentalized in brain, and that different brain areas control their glucose levels locally. For example, glucose drops are restricted to the hippocampus when the animal is performing a memory test, and are present despite constant peripheral glucose levels.

The BBB glucose transporter, GLUT1, is saturated at normal physiological glucose concentrations. Therefore, to acutely increase net glucose flux across the BBB, the number of GLUT1 proteins exposed to the blood must be increased. Dilatation of the capillary bed will expose more endothelial cells, with their corresponding GLUT1, to the blood, and thus increase the acute transport of glucose into the brain. However, the mechanisms responsible for regulating the rapid changes in local blood flow that are associated with brain activation are not yet well characterized. What is currently well described is that both individuals with T2DM and individuals with insulin resistance short of diabetes show impairments in endothelial-dependent vasodilatation. Consequently, given that cognitive testing leads to activation (and drops in the interstitial glucose levels in the areas activated), this endothelial dysfunction may lead to a 'functional hypoglycemia' and contribute, at least in part, to the cognitive deficits associated with diabetes and insulin resistance.

It is not known whether elevated cortisol levels affect glucose transport at the BBB (Figure 1). However, we know from animal studies that glucocorticoid exposure inhibits glucose transport into hippocampal neurons and glia. We also know that individuals with T2DM (and insulin resistance) have abnormalities in the HPA axis, particularly in feedback control. Consequently, we propose that, analogous to the reduced ability to locally increase glucose flux across the BBB with activation due to the reduced vascular reactivity in T2DM and insulin



**Figure 1** Representation of the blood and the brain compartments separated by the BBB. The green trapezoids represent the GLUTs. Reduced glucose transport across the BBB (step 1) and/or into the cells in the hippocampus (step 2), particularly during activation, may result in functional hypoglycemia and impaired memory performance. The sections of the bidirectional arrows pointing to the down red arrows represent known negative influences on glucose transport, and those pointing to the question marks represent a proposed negative influence that remains to be shown.

resistance, among individuals with elevated cortisol levels, there may also be a 'functional hypoglycemia,' this time at the neuronal level, also contributing to the cognitive deficits.

We propose that although this aggregate 'functional hypoglycemia' may be widespread in the brain, its damaging consequences may be at first more apparent in the hippocampus because of its high vulnerability to damage from hypoglycemia or other noxious influences. This hypothesized chronic low-grade 'functional hypoglycemia' may, in the long run, lead to hippocampal damage and volume loss.

It is also possible that chronic hyperglycemia is toxic to the microvascular endothelial cells, thus impairing transport of glucose across the BBB. Also, chronic hyperglycemia may be toxic to hippocampal cells directly by the increased production of damaging oxidative species resulting from increased metabolism based on increased intracellular glucose. However, this model, proposed by Brownlee to explain the tissue damage resulting from diabetes, does not offer an explanation for the damage associated with milder forms of insulin resistance, when glucose levels are still normal and there is only an elevation in fasting insulin levels. Future research will need to approach the problem more comprehensively, by evaluating multiple systems in the same individuals so as to better determine the relative contribution of each in the phenomenology expressed.

## Summary

Americans are living longer, which has contributed to the rising rate of age-associated diseases such as type 2 diabetes and dementia. This, coupled with the epidemic of obesity in industrialized nations, which will further add to an increasing number of T2DM cases within the overall population, makes improving our understanding of how type 2 diabetes affects the aging brain indispensable. In this article, we have reviewed the existing literature on brain aging, diabetes, and the stress regulatory system. There is increasing evidence that dysregulation of the stress and glucoregulatory systems interacts at multiple levels to exert a negative impact on human health in general, and on the aging brain in particular. Although a consensus has not yet gelled within the literature on the exact brain areas affected by the dysregulation of those systems, it is now clear that the MTL is likely the major brain region affected. Within the MTL, the hippocampus, a structure crucially involved in recent memory, appears to be particularly sensitive to these neuroendocrine abnormalities. Since MTL atrophy is also of relevance for MCI and AD, this might explain some of the recently reported associations between

dementia and type 2 diabetes. An enhanced understanding of the underlying pathological processes will allow the development of behavioral and pharmacological approaches targeted to protect the integrity of the hippocampus in older individuals. But there is much work to be done and additional progress in this research area is clearly warranted.

*See also:* Aging of the Brain and Alzheimer's Disease; Aging and Memory in Humans; Chronic (Repeated) Stress: Consequences, Adaptations; Cognition in Aging and Age-Related Disease; Dementia; Hippocampus; Hypothalamic–Pituitary–Adrenal (HPA) Axis; Metabolic Syndrome and Sleep; Stress and Neural Involvement in Metabolism; Stress and Cognition; Stress and Vulnerability to Brain Damage; Stress: Homeostasis, Rheostasis, Allostasis and Allostatic Load.

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