Neural Networks, Cognition, and Diabetes: What Is the Connection?

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Diabetes has been associated not only with subtle cognitive deficits in mental speed and flexibility (1,2) but also with an increased risk for development of significant disruption in cognitive function in the form of dementia (3). In order to prevent subtle cognitive sequelae and potentially reduce the burden of dementia on an aging world population (4), a better understanding of the pathophysiological mechanisms underlying the cognitive dysfunction in diabetes is needed.

There are several factors associated with diabetes and its management beyond acute metabolic or vascular insults that are potentially involved in this cognitive disruption, a few of which will be briefly reviewed here. Hyperglycemia may affect cognitive function by altering synaptic plasticity in the brain (5), increasing levels of oxidative stress (6), and/or subtly altering the cerebral microvasculature (7). Treatment of diabetes may lead to slight or occasionally more severe periods of hypoglycemia, which may translate to structural and metabolic alterations of the central nervous systems and subsequent cognitive dysfunction. However, it has been observed that subtle diabetes-related cognitive changes are associated with chronic hyperglycemia rather than episodes of hypoglycemia (8). The same study also observed that there was no significant difference in cognitive function between aggressively managed subjects with reduced levels of microvascular complications and those with a greater degree of microvascular complications. Other studies have observed this as well (9). This may indicate that the association between chronic hyperglycemia and subtle cognitive dysfunction is related to factors outside of microvascular complications alone. In this context, the potential impact of chronic exposure to endogenous or exogenous insulin above the normal physiological range should be critically evaluated.

Mild cognitive impairment is associated not only with age of diabetes onset and disease duration but also with insulin treatment (10). The risk of dementia is also highest in people with diabetes treated with insulin (11). Hyperinsulinemia in nondiabetic individuals has also been associated with cognitive impairment (12). This association is confounded by other comorbid factors, disease duration, and disease severity. However, there are several sound biological mechanisms by which prolonged hyperinsulinemia may influence central nervous system function. Not only is insulin a vasoactive substance (13), but it also inhibits "housekeeping" processes important for healthy brain aging (i.e., autophagy) (14) and influences processing of proteins related to Alzheimer disease (15). Prolonged exposure of the brain to higher than physiological levels of insulin may alter metabolic pathways in a manner that is deleterious to cognitive circuitry, given that this circuitry is dependent on cells influenced by these metabolic processes. These factors likely impact the changes associated with the phenomenon of "brain insulin resistance" observed in Alzheimer disease.

It should be noted that comorbid conditions and confounding variables such as hypertension, brain infarcts, dyslipidemia, obesity, socioeconomic status, depression, and levels of mental and physical activity must also be taken into consideration when discussing diabetes-associated cognitive dysfunction.

Any factor that precipitates cognitive dysfunction must affect brain circuitry in some manner. Given this necessity, one potential strategy for elucidating the relevant pathophysiological link between diabetes and cognitive dysfunction is to isolate the factors discussed above and compare their effects not only on direct cognitive measures or on the risk of developing cognitive impairment but also on measures of the neural networks that are affected. Neural networks have been shown to be acutely altered by structural lesions causing cognitive deficits (16) and are altered in at-risk populations prior to structural changes such as atrophy (17) before clinically measurable effects on cognition. Therefore, measures of neural networks may be best suited to track the earliest effects of diabetes on brain function. In this vein, the study presented in this issue of *Diabetes* by van Duinkerken et al. (18) lays the groundwork for these investigations. This study is an extension of their work investigating the neural network correlates of cognitive deficits observed in type 1 diabetes mellitus (T1DM), in which they hypothesize that these changes are modified by the presence of microvascular disease. Previously these investigators explored functional connectivity within neural networks using magnetoencephalography (MEG) (19) and concluded that "chronic hyperglycemia, among other factors, may negatively affect brain functioning even before microvascular damage becomes manifest." In the current study, the authors skillfully use functional magnetic resonance imaging (fMRI) in the absence of an experimentally predetermined task, also known as resting-state fMRI, but referred to herein as task-free fMRI (TF-fMRI). (Vemuri et al. [20] review the application of this technique in a related cognitive context.) TF-fMRI allows for greater spatial resolution and visualization of networks of synchronized activity in the brain (intrinsic connectivity networks [ICNs]) than typically achieved by MEG.

The authors used TF-fMRI to identify ICNs in 49 T1DM patients with microangiopathy (MA^+) and 52 without

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microangiopathy (MA^-) compared with 48 control (CN) subjects and their relationship to various cognitive and disease variables. They found increases in connectivity in visual processing and sensorimotor networks in MA^- not present in MA^+ relative to CN subjects, and decreases in connectivity in attentional, auditory/language processing, and executive control networks that progressed in degree going from CN>MA^-> MA^+. Given that the MA^+ subjects were significantly older and had greater depressive symptoms, higher systolic blood pressure, and an earlier disease onset and longer disease duration, a subsequent analysis was conducted matching 27 MA^+ and 28 MA^- on disease onset and duration. In this analysis, the increased connectivity in the MA^- group in the visual processing and sensorimotor networks was the only statistically significant finding. It should be emphasized that the MA^+ group did not differ from the CN group in these two networks (MA^+ results are reported as a relative decrease to MA^-, just as the CN group would appear as a relative decrease to MA^-, both of which being primarily driven by the MA^- group's increase in connectivity in these two networks).

This study will certainly advance the field in the search for pathophysiological mechanisms of cognitive decline in diabetes. The authors focused on a T1DM population, which may be less confounded by metabolic syndrome comorbidities than a type 2 diabetic population. They also had a relatively large sample of well-characterized subjects with expert acquisition and analysis of TF-fMRI data. The study's weaknesses lie in the inherent difficulties in this and other TF-fMRI studies. TF-fMRI is reliant on the blood oxygenation level–dependent signal and the fidelity of neurovascular coupling, which may be altered by microvascular changes. However, the similar results the authors report using MEG (which is not dependent on neurovascular coupling) are reassuring. In this regard, future TF-fMRI studies may benefit from inclusion of additional neuroimaging measures of white and gray matter integrity, which will also help tease apart other etiological factors. TF-fMRI also needs a model of the organization of the brain when it is not being experimentally directed (i.e., in a "resting state" during a task-free experimental paradigm). This will allow for a priori hypothesis generation and also circumvent some of the difficulties of TF-fMRI experimental design and interpretation.

One common difficulty in TF-fMRI interpretation is the phenomenon of increased functional connectivity, which is typically ascribed to "compensation." However, this link has not been firmly established nor is it based on a model of undirected brain activity measured by TF-fMRI. In Alzheimer dementia, the earliest functional changes detected in at-risk populations appear to be increases in functional connectivity in posterior limbic circuitry as early as the third decade of life (21). The same circuitry displays decreased functional connectivity later in life and is accompanied by increased functional connectivity in anterior/frontal limbic pathways (22), which in turn also decreases as Alzheimer disease progresses (23). Therefore, the increases in connectivity observed in the MA^- group studied by van Duinkerken et al. may be related to an intermediate stage of connectivity change. This is clearly evident in the networks displaying decreased connectivity in a dose-dependent manner going from CN>MA^-> MA^+. This line of reasoning is also supported by the fact that the difference between MA^+ and MA^- was not present when they were matched on disease duration and age of onset. Therefore, the results of this study do not strongly implicate microvascular disease as the only, or most prominent, factor related to diabetes-associated cognitive disruption. However, this study does implicate disease severity and duration, suggesting that metabolic derangements associated with chronic exposure to either hyperglycemia and/or hyperinsulinemia may be more prominent in the development of diabetes-associated cognitive decline.

Future studies should focus on differentiating the effects of chronic hyperglycemia and hyperinsulinemia on measures of neural network integrity. Such studies will not only advance our understanding of the pathophysiological mechanisms underlying the cognitive dysfunction in diabetes but will also refine the use of neural network metrics as biomarkers of cognition. This will facilitate tracking of neural network responses to early intervention strategies targeting key pathophysiological mechanisms before the appearance of any cognitive dysfunction, thereby refining strategies aimed at reducing the cognitive burden of diabetes.

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