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Preserving Cognition in Children With Diabetes: Do Alterations in Functional Network Connectivity Play a Role?

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COMMENTARY

Whether, and to what extent, type 1 diabetes (T1D) affects the brains of children and adolescents has been debated for more than 30 years. Early studies found that children and adolescents with T1D were more likely to perform somewhat poorer than their healthy peers on tasks of mental efficiency that required rapid responses and sustained attention, as well as on measures of executive functioning that required problem-solving and planning (1). It was assumed, but not proven, that these between-group differences were a consequence of differences in brain integrity. Only when researchers began using MRI techniques was there unequivocal evidence that diabetes in childhood is accompanied by gross structural changes to the brain, including relative reductions in gray matter density in multiple cortical regions and microstructural abnormalities in major white matter tracts (2,3). Furthermore, these effects were most pronounced in those who developed diabetes early in life and were evident within 2–4 years of disease onset (4–7).

One might expect that a significant loss of neurons, accompanied by axonal damage relatively early in life, would lead to increasingly serious cognitive impairment over time in people with diabetes. Interestingly, that does not appear to be the case. Cross-sectional studies of children and young adults with T1D do not show a significant worsening of performance with increasing age or disease duration (8), nor were marked declines in cognition seen in the adolescents and adults participating in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, despite more than 25 years of follow-up (9). One possible compensatory mechanism that could protect brain function in children with T1D has now been identified by Sagger et al. (10), who in this issue describe the first evidence of increased functional connectivity measured using resting-state functional MRI (rsfMRI) within a series of neuronal networks.

rsfMRI is a tool that is commonly used to assess the functional connections of the brain. It provides a measure of spontaneous brain activity forming spatially distinct networks, such as the default mode (monitoring internal and self-referential processes), attention, visual, and motor networks (11). Although this brain activity is unrelated to any task, it has been shown to be related to specific cognitive functions. Altered connectivity in adulthood has been associated with a number of diseases, including diabetes (12). Adult T1D patients with complications show decreased visual and motor network connectivity, whereas adult patients without complications show higher connectivity in such networks (13).

rsfMRI data can be analyzed in a data-driven way, i.e., by allowing software to identify spatially distinct resting-state networks. A commonly used method is independent component analysis. Originally used to identify artifacts in data, this method has also proved to be a useful tool in the detection of resting-state networks (11). This procedure results in a set of spatial components comprising voxels to which the fMRI signal correlates over time. The fMRI signal and the spatial layout of these resting-state networks are then calculated for every individual. Another way to analyze rsfMRI data is hypothesis driven. In this method, one or multiple regions of interest (ROIs) need to be identified a priori. ROIs can be regions that have previously been found to be affected by a certain disease. For each subject, the fMRI signal of this ROI is then correlated to the fMRI signal of all other voxels of the fMRI scan. This procedure results in a correlation map of the associations between the fMRI signal of the ROI and that of the rest of the brain. These correlation maps are then compared between groups to determine differences.

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Using both methods, Sagger et al. (10) consistently showed increased functional connectivity in several brain networks in the T1D group, as compared with patterns of functional connectivity in healthy comparison subjects. This suggests that in response to having diabetes, the functional brain networks of these young patients undergo a "remodeling" or functional reorganization, perhaps as a compensatory reaction to diabetes-associated alterations occurring within the central nervous system (Fig. 1). The metabolic and biomedical factors triggering this remodeling remain unclear, although a direct correlation with HbA_{1c} levels was not found in this study. Putative triggers include one or more episodes of ketoacidosis or hypoglycemia, extensive glycemic excursions, or other factors that could affect the integrity of the blood-brain barrier or initiate neuronal necrosis.

The implications of this increased connectivity remain a mystery. One hypothesis is that it may serve as a compensatory mechanism to prevent or slow cognitive deterioration. Indeed, Sagger et al. (10) demonstrated a correlation between higher connectivity and better cognitive scores, which was also observed in an earlier study in adults with T1D (13). Although Sagger's group failed to find statistically significant differences in cognitive performance between those with and without diabetes, the T1D group consistently performed more poorly, with an effect size (Cohen's d ~0.3) that is commonly seen in many other studies comparing people with and without diabetes (1,14). It may be that the increased connectivity is just enough to prevent performance from deteriorating into the "clinically impaired" range. Alternatively, the increased connectivity may be more effective in some children than in others, or the effect may not persist over time or after the development of diabetes-associated microvascular insults. The scatter plots in Fig. 3 of Sagger et al. (10) seem to support the notion that there may be wide individual differences. Roughly half the T1D group had cognitive scores below the mean of the control subjects, but a majority of those patients had positive connectivity values, suggesting that their higher connectivity may not be sufficient to ensure fully normal performance. It would be of interest to determine whether this subgroup of patients has diabetes-related characteristics that distinguish them from the patients for whom increased connectivity is correlated with better cognition.

In summary, Sagger et al. (10) have shown that the brains of young patients with T1D may be remarkably plastic and may have the capacity to reorganize themselves, which, in turn, may be associated with better cognitive functioning—at least in some individuals. It is now important to determine what causes this connectivity remodeling and why some children with higher levels of connectivity do not show better cognition.

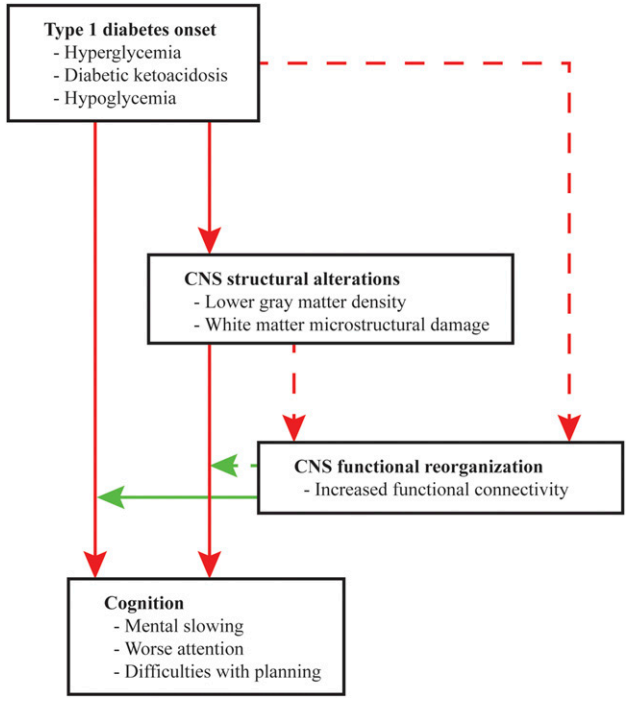

Figure 1—Schematic overview of how onset of T1D during childhood and adolescence may lead to cognitive decrements, either directly or through damage to the gray and white matter structure of the brain. Increased functional connectivity, in reaction to T1D itself and/or structural damage caused by T1D, may serve as a moderator variable to reduce the otherwise adverse impact of diabetes onset on cognition. The solid lines indicate the pathways that have been studied previously or were studied by Sagger et al. (10). The dashed lines are hypothesized pathways that warrant further study. The red arrows signify a negative effect, whereas the green arrows indicate the potential positive or ameliorative effects of increased connectivity on cognition. CNS, central nervous system.

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