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Glycemic extremes in youth with T1DM: Effects on the developing brain's structural and functional integrity

Ana Maria Arbelaez, M.D.¹, Katherine Semenkovich, B.A.¹, and Tamara Hershey, Ph.D.^{2,3,4}

¹Department of Pediatrics, Washington University School of Medicine St. Louis, Missouri, United States, 63110

²Department of Psychiatry, Washington University School of Medicine St. Louis, Missouri, United States, 63110

³Department of Neurology, Washington University School of Medicine St. Louis, Missouri, United States, 63110

⁴Department of Radiology, Washington University School of Medicine St. Louis, Missouri, United States, 63110

Abstract

Hypoglycemia and hyperglycemia are rare occurrences in normal individuals, but they occur commonly in patients with type 1 diabetes mellitus (T1DM) due to a dysfunction of peripheral glucose-insulin-glucagon responses and non-physiologic doses of exogenous insulin, which imperfectly mimic normal physiology. These extremes can occur more frequently in children and adolescents, due to events leading to the diagnosis of T1DM (prolonged untreated hyperglycemia, diabetic ketoacidosis), and to behavioral factors interfering with optimal treatment. Given that these events are occurring at a time of dynamic changes in brain structure and metabolic demand, it has been hypothesized that glycemic extremes could alter normal brain developmental trajectories depending on the age and severity at which these extremes are experienced. Researchers have attempted to determine the impact of diabetes, hypoglycemia, and hyperglycemia on brain structure and function *in vivo* using various neuroimaging techniques although few studies have examined these questions in children and youth with T1DM within a neurodevelopmental context. In this article, we review the current neuroimaging techniques available, describe the limited data in youth that address whether exposure to glycemic extremes in T1DM has any long-lasting consequences on the brain and its functions within a developmental perspective, and provide commentary on future directions for this field.

Keywords

brain; type 1 diabetes mellitus; children; neuroimaging; cognition

The adult brain accounts for a disproportionately large percentage of the body's total energy consumption (1). However, during brain development, energy demand is even higher, reaching the adult rate by age 2 and increasing to nearly twice the adult rate by age 10, followed by gradual reduction towards adult levels in the next decade (1-2). The dramatic changes in brain metabolism occurring over the first two decades of life coincide with the initial proliferation and then pruning of synapses to adult levels. The brain derives its energy almost exclusively from glucose and is largely driven by neuronal signaling, biosynthesis

and neuroprotection (3-6). Glucose homeostasis in the body is tightly regulated by a series of hormones and physiologic responses. As a result, hypoglycemia and hyperglycemia are rare occurrences in normal individuals, but they occur commonly in patients with type 1 diabetes mellitus (T1DM) due to a dysfunction of peripheral glucose-insulin-glucagon responses and non-physiologic doses of exogenous insulin, which imperfectly mimic normal physiology. These extremes can occur more frequently in children and adolescents with T1DM due to the inadequacies of insulin replacement therapy, events leading to the diagnosis (prolonged untreated hyperglycemia, diabetic ketoacidosis), and to behavioral factors interfering with optimal treatment. When faced with fluctuations in glucose supply the metabolism of the body and brain change dramatically, largely to conserve resources and, at a cost to other organs, to preserve brain function (7). However, if the normal physiological mechanisms that prevent these severe glucose fluctuations and maintain homeostasis are impaired, neuronal function and potentially viability can be affected (8-11).

Given that these events are occurring at a time of dynamic changes in brain structure and metabolic demand, it has been hypothesized that exposure to glycemic extremes during childhood could alter normal brain developmental trajectories (12) depending on the age and severity at which these extremes are experienced (13). Data suggest that early exposure to T1DM, and specifically to severe hypoglycemia, may lead to subtle differences in cognitive and academic function (14-26). However, our understanding of the neurobiological underpinnings of these cognitive differences in youth with T1DM is very limited. Researchers have attempted to determine the impact of diabetes, hypoglycemia, and hyperglycemia on brain structure and function *in vivo* using various neuroimaging techniques. This literature has been reviewed extensively in adults (27-29). However, despite advances in neuroimaging techniques amenable to studying children, relatively few studies using these techniques have been conducted in youth with T1DM and thus few reviews have examined these questions within a neurodevelopmental context (14,30) (**Table 1**). In this article, we review the current neuroimaging techniques available, describe the limited data in youth that address whether exposure to glycemic extremes in T1DM has any long-lasting consequences on the brain and its functions, and provide commentary on future directions for this field.

Brain Development

Brain synaptic development and metabolic demands vary throughout childhood and continue into young adulthood. Synaptic density increases rapidly during early postnatal cortical development, followed by a discrete period of synaptic pruning that typically occurs during adolescence (31-38). Synaptic and spine numbers subsequently stabilize during adulthood. Brain glucose metabolism (39) and oxygen consumption (40-41) follow a similar course with some regional variability (39), presumably reflecting associated changes in synaptic density and proliferation. From 2–3 months of age until 4 years of age, glucose use in the brain increases dramatically, until it is double the rate of the adult brain by the end of the first decade of life. It then begins to decline and reaches adult levels in the third decade of life, where it accounts for approximately 20% of the energy consumed in the body despite representing only 2% of the body weight (2).

In addition to changes in brain metabolism during development, there is a complex array of structural changes in the normally developing brain. Between the ages of 1-6 years old total brain volume increases, and by the age of six, it reaches about 90 percent of the adult brain volume (42-44). However, total gray matter volume, cortical volume and average cortical thickness increase in childhood up to ages 9-11, and then begin to decrease over the rest of childhood and adolescence as synaptic pruning occurs. In contrast, myelination of white matter (as reflected in white matter volume) increases gradually throughout childhood,

adolescence and even early adulthood (44) (Figure 1). In addition, within gray white matter, there is regional and sex-related variability in these developmental trajectories (45-46).

Many critical events in the evolution of T1DM disease co-occur with these dynamic developmental trajectories (Figure 1). T1DM can be diagnosed at any age, but incidence rates generally increase with age until mid-puberty and then decline (47). Similarly, glycemic extremes in T1DM can occur at any age, but a period of untreated hyperglycemia occurs prior to diagnosis and its risk is also higher during adolescence; while severe hypoglycemia is more likely to occur in younger children with T1DM or in those with tighter glycemic control. The co-occurrence of these events with the different neurodevelopmental processes may interact to produce either qualitatively or quantitatively different effects. This question has been discussed much in the T1DM literature, but few articles have directly addressed the issue (14,48-49). If there were critical developmental time periods when the brain was particularly vulnerable to severe hypoglycemia or hyperglycemia, then perhaps a rational argument for periods of tighter or looser control during some ages but not others could be made and outcomes could be improved.

Mechanisms of neuronal damage due to glycemic changes

Various mechanisms of how glycemic extremes might induce neuronal or axonal injury or dysfunction have been proposed (8-11). Neurons have a constantly high glucose demand. However, glucose uptake in neurons appears to be independent of insulin action. Thus, neuronal glucose uptake depends on the extracellular concentration of glucose (50-51), making them unable to efficiently down-regulate glucose transport inside the cell. This confers a higher risk for toxic effects in neurons vs. other cells from exposure to severe glycemic extremes and acute or chronic glycemic fluctuations (10-11). Glucose neurotoxicity could be induced through oxidative stress, which is promoted by glucose through a combination of free-radical generation and impaired free-radical scavenging ability (11). Induction of oxidative stress can generate more reactive molecules from glucose that combine with cellular and extracellular macromolecules, altering their functional properties and causing downstream adverse effects on cell function, which all lead to mitochondrial dysfunction and cell damage. Hypoglycemia has also been linked to overstimulation of N-methyl-D-aspartate (NMDA) receptors during episodes, resulting in excitotoxicity and cell death (21,52), although apoptotic mechanism have also been proposed (8-9,53). Furthermore T1DM is also associated with fluctuations of a number of endocrine factors (insulin, c-peptide, cortisol, IGF-1) and paracrine factors (ketone bodies, lactate), which may have complex effects on the brain development of children with T1DM (54-56).

Assessing the impact of the glycemic extremes in the developing brain

Assessing the impact of the glycemic extremes in the developing brain can be difficult due to the inherent glucose variability of the disease but more so due to the inability to precisely quantify the degree of exposure to these glycemic extremes. For example, the definition and severity of hypoglycemia is often disputed, inconsistent between studies and can be hard to confirm retrospectively. There are no laboratory tests to quantify past exposure, clinical recall is imperfect, and there can be unrecognized and unrecorded episodes, particularly when there is hypoglycemia unawareness from recurrent hypoglycemia and in young prepubertal children asymptomatic nocturnal hypoglycemic episodes are common (57-59). Furthermore, within groups of well-controlled patients with T1DM, the frequency of severe hypoglycemia events can be bimodal, with a large proportion reporting no previous events, and a few individuals having a large number of events. Severe acute hyperglycemia (with or without diabetic ketoacidosis) can also be difficult to characterize, unless patients were

hospitalized and full medical records are available. Chronic hyperglycemia exposure can be more easily captured through HbA1c levels, but only if they were routinely and reliably captured over the entire duration of diabetes. Researchers have attempted to weight degree of hyperglycemia experienced by the length of time it was experienced in order to get at a dose response/exposure score in different ways. Others have focused on variability of glucose levels over time, either from A1c levels or from short term continuous glucose monitoring. All of these efforts will at best be estimates of true exposure until affordable, reliable and non-invasive continuous blood glucose monitoring from diagnosis on is widely used. Nevertheless, some progress has been made in understanding the impact of these more traditional measures of glycemic extreme exposure on the brain through neuroimaging.

Modern neuroimaging techniques allow us to explore alterations in the brain's macrostructure (e.g. regional volumes and shapes) using standard magnetic resonance imaging (MRI)), microstructural integrity of white matter (using diffusion tensor imaging (DTI)), and the brain's activity at rest or in reaction to a specific challenge (using positron emission tomography (PET) and functional MRI (fMRI)) (60-61) presumably accumulated over time and after repeated exposure to extreme glycemic states. All these techniques rely on multiple assumptions and require careful and skillful interpretation of their findings to avoid false positive findings (type 1 error). Although these techniques can answer questions about how brain structure and function are affected by certain diseases or conditions, they cannot directly address the mechanisms by which these changes are produced and each has their own strengths and weaknesses. Given that MRI only requires a relatively short amount of time to acquire, uses no radiation or contrast agent, and has no known risks for human health it has been most widely used for studying children with T1DM. In contrast, PET is not appropriate for studying children due to inherent radiation exposure. Thus, assessment of the effects of glycemic extremes in the brain of children and adolescents with T1DM is restricted to measurements based on MRI techniques.

Glycemic Effects on Regional Brain Volumes

Structural MRI techniques allow for the measurement of whole brain and regional white and grey matter volumes. These volumes can be compared across groups and correlated with age or critical clinical variables (e.g. exposure to hypoglycemia or hyperglycemia). Studies have found lower regional gray matter volumes in children with T1DM compared to healthy controls (49,62-63) as well as a decrease in T2 relaxation time in subjects with T1DM, which was interpreted as being characteristic of normal aging and suggesting accelerated brain aging of T1DM children (49). However, only one study is truly prospective (62) and none have specifically examined the timing of exposure to glycemic extremes during development. Thus our understanding of the impact of T1DM, hypoglycemia and hyperglycemia on the dynamic developmental trajectory of gray and white matter volumes is still relatively limited.

Early MRI studies hypothesized that severe hypoglycemia might negatively affect hippocampal volumes in children with T1DM, based on case studies and animal models (8,64-66). One study found no differences in hippocampal volumes between those children with T1DM and a past history of hypoglycemic seizures and those with T1DM but without a hypoglycemic seizure history (67), and one found enlarged hippocampal volumes in those with three or more past severe hypoglycemic episodes (68). This latter study suggested that the hippocampus might react to hypoglycemia in a way that results in greater gray matter volumes (e.g. via reactive neurogenesis, gliosis, loss of synaptic pruning, compensation). However, the consensus from this limited body of work is that the hippocampus does not suffer long-term atrophic changes due to severe hypoglycemic events during development. Volumetric differences in other brain regions that are known to be acutely hypoglycemia

sensitive (69-72), such as the thalamus and medial prefrontal cortex, have not been explicitly studied in youth with T1DM.

More recent work has taken a whole brain approach, searching the entire brain for hypoglycemia-related volumetric differences in youth with T1DM. One retrospective analysis found lower gray matter volume in the left superior temporal cortex (26), one found lower thalamic gray matter (63), one found lower whole brain gray volume (73) in T1DM youth who had experienced severe hypoglycemia in the past compared to those who had not. Another cross-sectional study found decreased whole brain gray and white matter volume in children with T1DM who experienced hypoglycemic seizures (67). The single prospective study in this field found that severe hypoglycemia experienced between scans was related to reduced white matter volume growth in the parietal occipital cortex over a 2 year time period (62). Clearly, there is a lack of consistent findings of the impact of previous severe hypoglycemia on regional or whole brain volumes. This could be due to differences across studies in the ages studied, definitions of severe hypoglycemia, sample sizes, analytical approaches, or a failure to account for the ages at which severe hypoglycemia was experienced. It also indicates that, even if there truly are long-lasting effects of severe hypoglycemia on the macrostructural features of the developing brain, these are likely subtle.

Given that chronic hyperglycemia is a default state of T1DM and the most concerning for long-term consequences in other organ systems, its effects on the developing and aging brain have been of great interest. Degree of chronic hyperglycemia has been associated with both gray and white matter volume differences in youth with T1DM. A retrospective, whole brain analysis found that greater prior hyperglycemia was related to smaller right cuneus and precuneus cortical gray matter volume and smaller white matter volume in the right superior parietal region. Subthreshold results were also found in the homologous left sided regions in these areas (26). Both regions are adjacent to each other and reside in the parietal/occipital cortex. Replication of these findings in other samples of youth has been limited, although similar regional cortical findings also have been reported in adults with T1DM. One group of investigators found an association between decreased gray matter in the right cuneus and higher lifetime HbA1c averages (75-76) and another study found reduced gray matter density in the right occipital lobe in diabetic adults with retinopathy compared to healthy controls (77). The consistent effects of hyperglycemia on the macrostructure of the precuneus/cuneus region may suggest special vulnerability of this region to the neurotoxic effects of chronic hyperglycemia, particularly given that this region is highly glycolytic at rest (78).

More extreme hyperglycemia that includes diabetic ketoacidosis (DKA), which has been associated with subclinical cerebral edema (79-80), has not been analyzed separately in the existing volumetric MRI studies of youth with T1DM, perhaps due to difficulty in documenting and defining severity, or lack of exposure in those samples. However, neuroimaging studies in children with DKA have documented narrowing of the lateral ventricles in greater than 50% of children during DKA treatment (81), despite only mild mental status changes in these children. This supports a much greater incidence of subclinical cerebral edema in pediatric patients with DKA than was previously suspected.

Glycemic Effects on White Matter Integrity

Early neuroimaging studies of white matter typically used qualitative measures of white-matter hyperintensities. However, those methods are limited in sensitivity and the scope of white matter effects they can detect. Diffusion Tensor Imaging (DTI) provides a quantitative assessment of white matter integrity through the measurement of diffusion of water molecules in brain tissue. In white matter fibers, this diffusion is constrained and thus

directional; when degraded, diffusion is less constrained and more random (82-83). DTI is sensitive to subtle white matter brain injury in humans (84) and can detect changes even when standard T2-weighted images appear normal and the white matter region volumes are similar (85). In addition, DTI measures have been directly validated by means of comparison with immunohistochemical indicators of axonal injury in animal models (86). Just like brain volumes, white matter properties change dynamically during normal development and these processes need to be considered in group and individual level analyses.

Although the effects of severe hypoglycemia on white matter integrity have been examined in adults with T1DM, the issue has not been fully explored in children with T1DM. One retrospective analysis found no significant effects of severe hypoglycemia on white matter integrity across the brain in T1DM youth (87). As noted above, a prospective study found that exposure to severe hypoglycemia inhibited white matter volume development (62). Such changes could indicate that white matter integrity might also be affected over time, however, further prospective research using DTI is needed to test this hypothesis.

Given the impact of hyperglycemia on peripheral axonal integrity (88), it has been hypothesized that white matter integrity in the brain might also be affected. Many studies in adults with T1DM have explored this possibility, but to date there only two published studies in youth with T1DM. Exposure to chronic hyperglycemia, weighted by degree and duration (74) and repeated severe hyperglycemic episodes (most involving DKA) (87); were both associated with lower white matter structural integrity in and near the precuneus cortex. This study also found altered DTI parameters in the hippocampus and thalamus associated with severe hyperglycemia (87). This latter finding is notable because alterations in the thalamus have also been associated with T1DM and glycemic exposure in other imaging and neuropathological studies of adults (75,89-90) and youth (63). Specifically, DKA has been reported to acutely affect the diffusivity of the thalamus in a pediatric population (91-92). Importantly, severe hyperglycemia and DKA can affect water accumulation in the brain (edema) leading to altered DTI parameters which tend to normalize once DKA has resolved (93). Our findings suggest that the thalamus may exhibit long-term consequences of diabetes-related complications, such as multiple severe hyperglycemic episodes (87). Differences in DTI parameters in gray matter regions could reflect either direct pathologic damage or secondary degeneration due to the disruption of white matter tracts linking these structures to other areas (94).

Effects on Brain Metabolite Concentrations

Magnetic Resonance Spectroscopy (MRS) is similar to MRI in that it also depends on the signaling of hydrogen protons. However, while MRI uses the signaling of hydrogen protons to construct structural images of the brain, MRS uses such signaling to determine the concentration of brain metabolites in certain areas of the body. MRS examines concentration of metabolites including N-acetyl aspartate (NAA), lactate, choline (Cho), and Creatine (Cr). Increases or decreases in metabolites in the brain can signal various phenomena, such as neuronal integrity. Even though there are many benefits of MRS, such as the fact that it can be performed quickly and is low in cost, MRS also has limitations. One limitation is that it is not very specific; many artifacts appear on MRS scans performed on tissue close to bone or air, which makes obtaining images of brain regions close to areas such as the base of the skull challenging (95). In addition, MRS can only sample one or two broad regions of the brain at a time and thus cannot perform whole brain analyses.

Not many studies have used this imaging method in children with T1DM. However some have explored if differences in the metabolic milieu exist between T1DM and controls. One study found that children with T1DM had a lower NAA/Cr and Cho/Cr ratio in the pons and

a lower NAA/Cr ratio in the posterior parietal white matter compared to healthy controls (96). Decreases in NAA metabolites may indicate a loss of neurons, while a decrease in Cho may be due to a change in membrane lipids or a decrease in membrane turnover. However, they did not find a significant association between hyperglycemia or the number of previous hypoglycemic episodes and the ratio of metabolite concentrations in the brain (96). Others explored if there are regional differences between brain metabolites of children with T1DM compared to healthy control children 12 years after diagnosis (63), and found a decrease in NAA in the frontal lobes and basal ganglia, and greater Cho in the temporal and frontal lobes and basal ganglia compared to controls. Suggesting a loss of neuronal cells in the regions of the frontal lobe and basal ganglia as well as an increase in membrane turnover in the temporal, frontal lobes and basal ganglia. Others have used MRS to examine the impact of acute DKA on metabolites and chart recovery after treatment as well (97-98). One study found that during treatment for DKA there was a lower NAA/Cr ratio in periaqueductal gray matter and occipital gray matter compared to the recovery phase (98). It was not possible to compare baseline (pre DKA) to post-DKA scans, thus it is unclear if there are any long-term consequences of DKA (or chronic hyperglycemia) on MRS measured metabolites.

Effects on Brain Blood Flow

Changes in local blood flow (measured directly with PET or indirectly with Arterial Spin Labeling (ASL-fMRI)) can provide a surrogate marker of global or regional neuronal activation during different cognitive tasks, pharmacologic challenges, or glycemic extremes such as hypoglycemia (69-71), hyperglycemia or hypoglycemia associated autonomic failure (HAAF) (99). An increase in regional cerebral blood flow (rCBF) is thought to reflect increases in neuronal activity primarily in the terminal fields (100), due to increases in synaptic metabolic activity, but not in the spike firing rate. Interpretation of these changes depends on whether there are inhibitory or excitatory (101) input pathways to the region, as increases in both can cause increased blood flow (102). Furthermore, they could reflect dysfunction of a particular brain region or network that is not necessarily visible as a structural defect. When interpreting these data, it must be determined whether the challenge given (e.g. drug, hypoglycemia) changes whole brain blood flow, so that relative regional blood flow changes can be properly normalized. PET methods unfortunately are invasive and require the use of radioactivity, which makes them inappropriate for use in children and adolescents. ASL-MRI, in contrast, is non-invasive, does not require radiation, and can be repeatedly performed on the same subject; therefore it can be used in children. We found comparable blood flow estimates during hypoglycemia using ASL-MRI and PET, demonstrating that such methods are likely replicable (70). However, ASL requires a very high signal-to noise ratio and cannot accurately map either low (10 mL/100g/minute) or high (150 mL/100 g/minute) rCBF states. To our knowledge, this technique has not yet been used in studies of children with T1DM.

Effects on Brain Metabolism

When a brain region is active in performance of a task, or in response to a physiologic change such as hypoglycemia, there will be a change in metabolism in the neurons in that region, which can be imaged by PET using radioactively labeled glucose analogues. These analogues are taken up by cells as native glucose but are either arrested early in the intracellular metabolic pathway and retained within the cells for longer (if using fluorodeoxy glucose (FDG)) or incorporated into the glucose metabolism pathways (if using 1-C¹¹ labeled glucose). The tracer uptake can be modeled mathematically to derive measures of glucose uptake, content, and cerebral metabolic rate (103-105). Although these are great methods to assess mechanistic questions related to diabetes pathophysiology, their use is limited to adults with intact renal function due to the exposure to radioactivity, and invasiveness of the studies.

Effects on Brain Function and Functional Connectivity

Functional MRI allows us to measure the brain's blood flow response to different tasks, and its resting state functional organization. Task based studies must consider changes in the subjects' behavior across stimulation conditions as a potential confounder when interpreting findings. If the goal of a study is to assess the neuropathophysiology of a condition such as hypoglycemia, changes in behavior within the scanner across conditions or groups could make such conclusions difficult. For example, if a subject performs differently on a cognitive challenge while hypoglycemic compared to while euglycemic, differences in brain activation patterns between the two conditions could have little to do with the direct action of hypoglycemia on brain pathways, but instead could merely reflect the effects of poor performance or difficulty level on brain activity. Functional connectivity analyses (based on resting state blood oxygen level-dependence (BOLD)) avoid this potential performance confound. Furthermore, resting-state fMRI BOLD signal might relate to the underlying metabolism of the brain and, in particular, glycolysis. A regional increase in metabolism (particularly in glycolysis) can significantly exceed the change in oxygen consumption (106). This change in oxygenation status can be captured using BOLD MRI, which depends on the difference in magnetic signal generated by deoxyhemoglobin vs. hemoglobin. Functional networks and BOLD signal can be altered by disease states, including T1DM. Researchers have found that adults with T1DM with microangiopathy have decreased functional connectivity between brain regions involved in working memory (the left frontoparietal network), language (the left supramarginal gyrus), attention (the left temporal pole, and inferior and superior frontal gyrus), motor control (the motor cortex, and pre and post central gyri) and visual processing (the visual cortex) (107). However, to our knowledge, there are no published fMRI-BOLD studies in children with T1DM.

Differences in the central nervous system in diabetes have been linked to severe hypoglycemia, severe hyperglycemia and chronic exposure to hyperglycemia in children. Although there are diverse findings across these studies, there does seem to be an emerging consensus that the posterior cortical regions of the brain, most commonly the precuneus/cuneus cortex, may be most commonly affected by hyperglycemia in children and adults (Figure 2). The precuneus/cuneus region has many interesting properties that could provide the basis for its vulnerability to hyperglycemia. This region is a critical player in the "default mode network" or DMN. Regions in this network (precuneus/cuneus/posterior cingulate, medial prefrontal, medial temporal and lateral temporal/parietal cortex) are highly active at rest (the brain's 'default' state; as measured by PET blood flow and glucose metabolism), but dramatically decrease activity during goal-oriented tasks (108-111). Regions in this network also have high functional connectivity as detected by resting state fMRI (rs-fMRI) (112). Further, the precuneus/cuneus is somewhat unique within the default network in that it shares with the primary visual cortex the highest baseline metabolism of the whole brain, and is the most functionally and structurally 'connected' part of the brain (113-114). Recent data has demonstrated that the precuneus/cuneus and the default network have the highest resting state glycolytic rate in the brain, a feature distinguishing them from the primary visual cortex (78). Finally, it is also one of the regions most affected in early Alzheimer disease (115) for which diabetes is thought to be a risk factor (116-117). It is possible that the high baseline demand on blood flow and glucose supply in the DMN may create a heightened vulnerability to alterations in blood glucose delivery (118). Regions of high aerobic glycolysis, such as the precuneus region, may be more vulnerable to this disruption, or disruption could be more likely to lead to cell dysfunction and ultimately cell death. However, it is unclear how developmental processes may be involved in any of these hypothesized effects.

Functional correlates of neuroimaging findings

The relationship between the described brain differences and cognitive, academic and occupational function in youth with T1DM have yet to be determined. Although there is ample evidence to suggest that children with T1DM have differences in cognitive functioning depending on their exposure to glycemic extremes, these data have not been linked to observed brain structural or functional differences in any coherent way. Cross-sectional, retrospective studies find that a higher rate of severe hypoglycemic exposure is associated with poorer cognitive function, particularly memory and attention, even when controlling for age of onset and hyperglycemia exposure (19,119-122). Meta-analyses have identified a medium effect size for the relationship between severe hypoglycemia and lower memory performance and small to medium effect sizes for learning, intelligence and verbal tasks (123). Further, effects on memory appear to be modulated by the timing of hypoglycemia, with earlier exposure leading to worse outcomes (120). Prospective studies are less common, and primarily represented by Northam et al's work in assessing a large sample of newly diagnosed children with T1DM and community controls over 12 years (63). Importantly, at diagnosis, children with T1DM did not perform differently than their control group on any cognitive test (124). After 12 years of diabetes, severe hypoglycemia exposure in the past was related to working memory, speed of processing and verbal skills whereas hyperglycemia was related only to working memory (125). An important caveat to these findings is that the test battery given had to change over time and the analyses presented are necessarily cross-sectional, and thus do not reflect within-subject change. In addition, the data have not been analyzed with respect to the timing of hypoglycemia exposure during development. Nonetheless, this study strongly supports the concept that severe hypoglycemia and hyperglycemia exposure during childhood predict cognition outcomes. Other work has suggested that children with T1DM have lower academic performance in school than controls (126-128). Elucidation of the role hypoglycemic and hyperglycemic episodes play in development of specific cognitive defects and how these lead to reduced academic performance is needed to merge these two lines of work.

Conclusions

Research to date examining the effects of hypoglycemia and hyperglycemia on brain structure and function allow us to make several tentative conclusions and point out several gaps in the literature. Over the past decade, much progress has been made in understanding the effects of glycemic extremes on brain structure and function in adults and to a lesser extent in youth. The work that does exist suggests several potential conclusions and areas of needed future study. First, there are relatively subtle, though detectable relationships between glycemic extremes and brain function and structure in youth with T1DM. Second, the pattern of regional brain effects appears different depending on which glycemic extreme is examined. However, in practice, most children have exposure to both glycemic extremes. It may be more clinically relevant — though also much more statistically challenging — to consider the interactive effects of both glycemic extremes over time. Similarly, the effects of DKA or interactions between DKA and other glycemic exposures have not been well addressed in existing analyses. Third, it is not fully understood whether these relatively subtle brain differences are the cause of the cognitive and academic differences reported, and if these effects have a clinically significant impact on daily function. Fourth, there is insufficient evidence regarding whether the timing of exposure to glycemic extremes modulates effects on brain structure and function. Researchers continue to define the fluid, non-linear and diverse trajectory of brain and cognitive development in normal children. More complete understanding of this complex process and its normal variation is necessary before one can fully understand any systematic alterations that may occur in children with T1DM due to glycemic extremes. Fifth, longitudinal, prospective assessment over a wide

age range and glycemic experiences is necessary to establish whether glycemic extremes precede brain volume and function changes or whether brain volume changes precede or are unrelated to glycemic extremes. These types of studies are underway in young children with T1DM (U10 HD41890), newly diagnosed children with T1DM (R01 DK064832), and older school aged children and adolescents with T1DM (R01 DK064832 (62). However, determining the effects of specific variables on brain development remains a challenge even in prospective studies, when there are many interacting factors that can influence brain development and functional outcomes, such as nocturnal hypoglycemia, environmental enrichment, life stressors, etc., many of which can be hard to measure accurately. Forthcoming analyses from these groups will begin to answer these difficult questions in a more conclusive manner. The important challenge in this field is to turn these primarily descriptive results into mechanistic, testable hypotheses. To do this, we will need to be careful not to force new data to fit with old hypotheses and instead be willing to accept more complex and nuanced patterns and interactions. By doing so, we may be able to identify networks of critical, glucose-influenced structures and construct optimized treatment protocols over different developmental time periods.

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Figure 1.

Schematic representation of the known normal trajectory of whole brain glucose consumption, and whole brain white and gray matter volume during childhood and adolescence. These trajectories are dynamic during the time frame of exposure to many type 1 diabetes-related glycemic extremes.

Effects of glycemic extremes on the developing brain

Figure 2.

A) Schematic representation of brain regions in young individuals with T1DM affected by hypoglycemia (green) (thalamus and hippocampus) and hyperglycemia (red) (cuneus and precuneus). Sagittal midline view. B) Schematic representation of brain regions in young individuals with T1DM affected by hypoglycemia (green) (temporal-occipital-prefrontal cortex) and hyperglycemia (red) (prefrontal cortex) lateral view.

Table 1

Summary of published neuroimaging papers examining the relationship between a history of severe hypoglycemia and hyperglycemia exposure and brain structure and function in youth with type 1 diabetes. (No evidence available about DKA).

First Author	Year	Groups	N	Age Range (years)	Neuroimaging variables examined	Effects of past severe hypoglycemia	Effects of past hyperglycemia
*Perantie (26)	2007	T1DM Controls	108 51	7-17	Voxel-wise gray and white matter volume; multiple comparison correction	Greater number of severe hypoglycemic episodes related to reduced volume in left superior temporal region	Weighted A1c associated with reduced volume in cuneus, precuneus; larger gray matter in PFC
Ho (73)	2008	T1DM	62	Mean age = 10	Clinical reading, hippocampal volume, total gray, white matter volume	Hypoglycemia seizure history associated with lower total gray matter	Hyperglycemia not analyzed
Northam (63)	2009	T1DM Controls	79 51	Mean age= 20	Voxel-wise gray and white matter volume and MRS	Reduced thalamic gray matter volume	Higher glucose level was associated with elevated myoinositol and decreased T2 in thalamus
*Hershey (68)	2010	T1DM Controls	95 49	7-17	Hippocampal, whole brain volumes	Greater number of severe episodes related to <u>larger</u> hippocampal volumes	No relationship to weighted A1c
+Aye (67)	2011	T1DM Controls	27 18	3-10	Whole brain gray and white matter volume; hippocampal volume	Smaller whole brain gray and white matter volume in those with hypo seizures	No relationship to weighted A1c
*Perantie (62)	2011	T1DM Controls	75 25	7-17	Voxel-wise gray and white matter volume; multiple comparison correction; Prospective analysis	Presence of severe hypo associated with reduced white matter volume over time in occipital-parietal cortex	Weighted A1c related to greater decrease in whole brain gray matter over time
+Aye (74)	2012	T1DM Controls	22 14	3-10	Diffusion tensor imaging; voxel-wise; multiple comparison correction	None	Weighted A1c correlated with radial diffusivity.
*Antenor-Dorsey (87)	2013	T1DM Controls	73 30	9-22	Diffusion tensor imaging; region of interest & voxel-wise; multiple comparison correction	None	No relationship with weighted A1c. DKA episodes included in severe hyperglycemia category. Greater number of severe hyperglycemic episodes related to lower white matter microstructural integrity in superior parietal lobule, hippocampus.

Overlapping cohort from Hershey Lab at Washington University

+Overlapping cohort from the Aye Lab at Stanford University