Brain Function Differences in Children With Type 1 Diabetes: A Functional MRI Study of Working Memory

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PATHOPHYSIOLOGY

Glucose is a primary fuel source to the brain, yet the influence of dysglycemia on neurodevelopment in children with type 1 diabetes remains unclear. We examined brain activation using functional MRI in 80 children with type 1 diabetes (mean ± SD age 11.5 ± 1.8 years; 46% female) and 47 children without diabetes (control group) (age 11.8 ± 1.5 years; 51% female) as they performed a visuospatial working memory (N-back) task. Results indicated that in both groups, activation scaled positively with increasing working memory load across many areas, including the frontoparietal cortex, caudate, and cerebellum. Between groups, children with diabetes exhibited reduced performance on the N-back task relative to children in the control group, as well as greater modulation of activation (i.e., showed greater increase in activation with higher working memory load). Post hoc analyses indicated that greater modulation was associated in the diabetes group with better working memory function and with an earlier age of diagnosis. These findings suggest that increased modulation may occur as a compensatory mechanism, helping in part to preserve working memory ability, and further, that children with an earlier onset require additional compensation. Future studies that test whether these patterns change as a function of improved glycemic control are warranted.

Type 1 diabetes is among the most common and chronic endocrine disorders, affecting an estimated 1.2 million American children and adults (1). Although technological advances have improved diabetes management, children living with this condition continue to experience overall poor glycemic control, with less than 17% of children with type 1 diabetes meeting the American Diabetes Association's designated goal for an HbA_{1c} of <7.5% (2).

The issue of whether dysglycemia in type 1 diabetes has a maladaptive effect on neurodevelopment has attracted the attention of both endocrinologists and neuroscientists. Children with early-onset type 1 diabetes—generally defined as an onset prior to ages 4–7 years (3–5)—have been the subject of particular focus, with greater cognitive impairment and reduced academic performance observed in these children relative to those with a later onset (3,4). Behavioral studies focused on identifying cognitive alterations experienced by individuals with type 1 diabetes more broadly have reported mild impairments in executive functioning, including working memory (6). Understanding the mechanisms underlying these alterations is important given the high cognitive load required for optimal adherence to a complex treatment regimen (7), as well as findings indicating that increased executive function may be associated with better disease management (8).

Structural neuroimaging studies have suggested a possible neural basis for type 1 diabetes–associated differences in executive function. We and others (9–13) have shown that young children with type 1 diabetes exhibit widespread differences in regional brain morphology

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relative to control subjects without diabetes, including in regions underlying executive function—the prefrontal cortex and anterior insula—as well as the occipital cortex and cerebellum (9,10). We also reported, as part of the Diabetes Research in Children Network (DirecNet), alterations in white matter (11–13) as well as reduced network efficiency (14).

Adding to these investigations are neuroimaging studies that examine brain function. Two reports have observed increased activation in executive function networks of adults with type 1 diabetes as they engaged in working memory tasks (15,16). Diabetes-related increases in neural responses during working memory processing have also been reported using magnetoencephalography (17). Of note, these studies documented activation differences despite equivalent behavioral performance between the diabetes and control groups. Such a pattern has led to the suggestion that heightened activation in type 1 diabetes may reflect a compensatory mechanism whereby increased brain function acts to facilitate normative behavioral performance. Similar compensatory alterations in activation are posited to play a role in other conditions, including attention-deficit/hyperactivity disorder (18), multiple sclerosis (19), β-amyloid plaques (20), and concussion (21).

Whether compensatory increases in activation of working memory networks are present in children with type 1 diabetes is not yet known. The current investigation therefore examined brain function in children with type 1 diabetes and age- and sex-matched healthy children (control group) as they performed a visuospatial working memory N-back task. A unique aspect of our study involves the use of three different working memory load conditions (0-back, 1-back, 2-back), which allowed for the application of a specialized method, known as parametric modulation, that identifies areas of the brain showing an increase in activation with increasing task difficulty. We hypothesized, based on previous research, that both groups would perform equally well in each of the three working memory load conditions but that children with type 1 diabetes would exhibit an increase in activation—more specifically, increased modulation of activation (i.e., exhibit a greater increase in activation with increasing working memory load)—in frontoparietal brain regions subserving working memory processing. We additionally explored whether these differences in activation were associated with measures of glycemic control and cognition.

RESEARCH DESIGN AND METHODS

Participants

This study was approved by the institutional review boards at each of the five participating DirecNet research centers and by the National Institutes of Health (NIH)-designated Data Safety Monitoring Board. Parents or legal guardians provided written informed consent and participants provided assent according to local guidelines. Details on the DirecNet study group and on inclusion and exclusion criteria for participants are included in Supplementary Material.

A total of 131 participants with type 1 diabetes and 66 control subjects from the five participating sites underwent MRI scanning. Fifty-one participants in the diabetes group and 19 control subjects were excluded due to one or more factors, including motion artifacts (28 participants with type 1 diabetes, 7 control subjects), anatomical abnormality (2 participants with type 1 diabetes), and errors in behavioral data recording (5 participants with type 1 diabetes, 6 control subjects), or because the participant was not performing the task as instructed (i.e., performed the task at or below chance level [16 participants with type 1 diabetes, 6 control subjects]). Therefore, the final imaging and behavioral data analyses included 80 participants with type 1 diabetes (mean ± SD age 11.5 ± 1.8 years; 46.3% female) and 47 control subjects (age 11.8 ± 1.5 years; 51.1% female). A χ^2 test indicated that the proportion of participants included versus excluded did not vary as a function of group ($\chi^2 = 1.971$, $P = 0.160$). Exploratory analyses testing whether included and excluded participants differed with respect to demographic and cognitive metrics were not significant (P values >0.192) (see Supplementary Material).

Cognitive Testing and Glycemic Measurements

All parents completed the Behavior Rating Inventory of Executive Function (BRIEF) (22) to assess children's executive functioning in daily life. As part of a larger neurocognitive test battery, children were administered the Working Memory Index of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (23), as well as the Spatial Relations and Concept Formation subtests of the Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III) (24), to assess visuospatial abilities and inductive reasoning, respectively.

A hyperglycemic index was determined for participants with diabetes based on all available HbA_{1c} values since diagnosis up to the time of participation in this study. This index, henceforth referred to as lifetime averaged $HbA_{1c}AUC_{6\%}$, was calculated as previously described (25) by computing the total area under the curve (AUC) >6.0% according to the trapezoid rule and dividing this value by the duration of time between diagnosis and the time of assessment. A continuous glucose monitoring (CGM) device (Medtronic iPro or Dexcom G5 or G6) was worn with the goal of acquiring at least two separate 6-day measurement periods within 90 days of the scan. A minimum of 72 h of CGM data including at least 24 h of overnight data per wear was considered acceptable. Covariates of interest were computed from CGM data including mean blood glucose (gluMean), two measures of glycemic variability (the coefficient of variation [CV] of blood glucose and the mean amplitude of glycemic excursions [MAGE]), and two measures reflecting percentage and severity of blood glucose values in hyperglycemic and hypoglycemic ranges (blood glucose AUC >180 mg/dL [AUC180] and blood glucose area over the curve <70 mg/dL [AOCBelow70], respectively).

MRI Acquisition

Participants were prepared for scans (unsedated) through scan simulation procedures prior to MRI scan as previously described (26). Children were scanned at each of five imaging sites using identical Siemens 3T TIM Trio whole-body magnetic resonance systems with matching 12-channel head coils and imaging protocols. T1-weighted structural images of the brain were acquired sagittally, right to left, using a magnetization-prepared rapid gradient echo sequence, with slice thickness 1 mm, repetition time 2,300 ms, echo time 2.98 ms, inversion time 900 ms, flip angle 9°, field of view 25.6 cm × 24 cm, 160 slices, matrix 256 × 256, voxel size 1 × 1 × 1 mm, and scan duration 4 min and 54 s. A T2*-weighted echo planar imaging pulse sequence was used for functional imaging while participants performed the working memory task with the following parameters: repetition time 2,000 ms, echo time 27 ms, flip angle 80°, field of view 22 cm × 22 cm, 33 slices, matrix 74 × 74, n frames = 246, voxel size 3 × 3 × 4 mm, and scan duration 8 min and 12 s. Immediately before and after the scan, blood glucose levels were measured in participants with type 1 diabetes to ensure the glucose levels were between 70 and 300 mg/dL. These two measurements were averaged together to compute the blood glucose level at the time of scan.

Functional MRI Task Design

During the functional MRI (fMRI) scan, participants performed a visuospatial multilevel N-back task (Fig. 1). In this test of working memory, participants were required to monitor a series of stimuli and to respond using a button press whenever a circle (henceforth referred to as the "target" stimulus) was presented in the same position on the screen as the one previously presented one or two trials back (henceforth referred to as "1-back" and "2-back," respectively). During the control condition, participants were required to press when the target was presented in the center of the screen during the current trial (henceforth referred to as "0-back"). Stimuli were presented in a block design. A total of twelve 35-s-long blocks were presented, including three 1-back, three 2-back, and six 0-back blocks. Each block contained a total of 14 trials, each consisting of a specifically positioned circle for 1.5 s, followed by a fixation cross for 1 s. The run time of the task was 8 min and 12 s. Responses and reaction times were recorded.

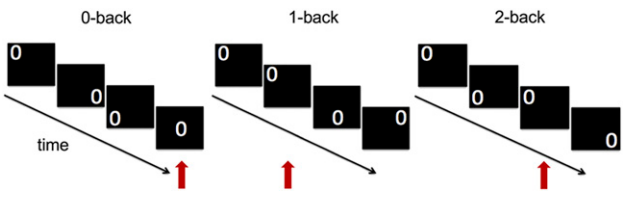

Figure 1— Visuospatial working memory (N-back) task. Participants were required to monitor a series of stimuli and to respond using a button press whenever a circle was presented in the center of the screen (0-back) or in the same position as the one or two previous screens (1-back and 2-back, respectively). Red arrows indicate timing of correct button press.

Behavioral Data Analysis

Statistical analyses of N-back performance were conducted using linear mixed-effects regression in R (version 3.6.1; R Core Team [27]) to assess group differences in accuracy, reaction time to correct trials, and the signal detection measure, d'. d' is computed through subtracting the z score of the false alarm rate (e.g., commissions) from the z score of the correct response rate (e.g., hits) and represents a preferred measure of working memory performance (28), since it takes into consideration both the relative frequency of correct hits and correct rejections. A high d' value indicates that the participant correctly responded to a high number of targets and appropriately withheld a response to a high number of nontargets, whereas a low d' value signifies that the participant responded to fewer number of targets (omission errors) and/or failed to withhold a response to a greater number of nontargets (commission errors).

Accuracy, reaction time, and d' were entered as the dependent variable in separate regression models. Working memory load (0, 1, or 2), sex, age, and group (diabetes, control) were entered as independent variables. The interaction of group and working memory load was subsequently added to each model to examine whether group differences in performance, if present, varied as a function of task condition. Significance for these and all other analyses was established based on a two-tailed α level of 0.05. For dependent variables with a nonnormal distribution (as indicated using the Shapiro-Wilks test), bootstrapping was used to compute 95% CIs for model estimates. The number of bootstrap samples was set to $n = 10{,}000$.

fMRI Data Analysis

Imaging data were preprocessed with FMRIB Software Library (FSL), version 5.0.8 (www.fmrib.ox.ac.uk/fsl). Details on preprocessing methods are provided in the Supplementary Material. Time-series statistical analyses of preprocessed data were carried out at the intrasubject level using a parametric modulation approach to identify brain areas in which neural activity varied as a function of working memory load. This approach, which enables characterization of responses along the dimension of task difficulty but does not allow for overall direct group comparisons within discreet working memory load conditions, was accomplished using a general linear model wherein the experimental regressor of interest was weighted by the mean-centered working memory load (0, 1, 2). Two regressors of noninterest (the instruction cue and the unmodulated working memory load) modeled the other portions of the experiment (29). Additional regressors of noninterest modeled six standard motion correction parameters as well as time points that exceeded a motion

threshold (75th percentile plus 1.5 times the interquartile range) defined by FSL's motion outliers tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). Information on motion for each group, including the number of frames flagged by the motion outliers tool, can be found in Supplementary Material. Each regressor was modeled using a synthetic hemodynamic response function and its first derivative. Results from within-subject analyses consisted of subject-specific parameter estimate maps of areas in which activation changed as a function of an increase in working memory load. These unthresholded parameter estimate maps were carried to higher-level analyses to assess between-group differences in neural modulation using FMRIB's Local Analysis of Mixed Effects (FLAME) (30). Within- and between-group analyses controlled for age, sex, and scan site. Results were visualized using a threshold of $Z > 3.1$, and a cluster probability of $P < 0.01$, corrected for whole-brain multiple comparisons using Gaussian random-field theory (31).

Exploratory Analyses: Associations Among Neural, Clinical, and Behavioral Measures

After checking distributions with the Shapiro-Wilks test, and transforming data if necessary, we conducted bivariate Pearson correlations separately within each group to examine associations between fMRI activations and clinical, behavioral, and cognitive measures. For reduction of the number of multiple comparisons, a single activation metric describing modulation strength across all regions identified in our primary analyses (testing a main effect of group on modulation of activation in voxel-based analyses) was computed for each subject. Prior to correlation, single subject modulation estimates (representing activation change with increasing working memory load) were adjusted for age, sex, and scan site using regression analyses. Specifically, age, sex, and scan site were regressed onto modulation estimates and unstandardized residuals were saved for use in correlations. Clinical, behavioral, and cognitive metrics were adjusted for age and sex when appropriate. Associations with MAGE were examined with and without adjustment for gluMean to discriminate the effects of glucose variability from glucose mean. For estimation of the significance of between-group differences in correlation coefficients, Fisher *r*-to-*z* transformation was performed.

Data and Resource Availability

The data sets generated during or analyzed during the current study are not publicly available, since they contain protected health information. De-identified data are available from the study group's Imaging and Data Coordinating Center (reikor@stanford.edu) upon reasonable request.

RESULTS

Participants

The diabetes and control groups did not differ with respect to age, $U = 1{,}759$, $P = 0.546$, or sex, $\chi^2 = 0.275$, $P = 0.600$ (Table 1). Six sibling pairs, discordant for diabetes, were included in the study sample. When unaffected siblings from each of the six sibling pairs were removed from the sample, all findings presented below remained unchanged. The mean age at type 1 diabetes onset was 4.8 ± 2.3 years. Ten children with type 1 diabetes (12.5%) had experienced one or more episodes of severe hypoglycemia (SH) since diagnosis; 22 (27.5%) had experienced one or more episodes of diabetic ketoacidosis (DKA).

Task Performance

Accuracy, reaction time of correct trials, and d' values are presented in Table 2. Across groups, increased working memory load was associated with reduced d' (1-back vs. 0-back β −0.64, 95% CI −0.93 to −0.36; 2-back vs. 0-back β −2.07, 95% CI −2.34 to −1.80), longer reaction time (1-back vs. 0-back β 47.26, 95% CI 19.98–73.80; 2-back vs. 0-back β 128.37, 95% CI 96.99–159.51), and reduced accuracy (1-back vs. 0-back β −0.03, 95% CI −0.04 to −0.02; 2-back vs. 0-back β −0.13, 95% CI −0.14 to −0.11). Increased age was also associated across both groups with higher d' (β 0.12, 95% CI 0.06–0.19), shorter reaction time (β −31.11, 95% CI −38.64 to −23.55), and increased accuracy β 0.008, 95% CI 0.005–0.012). Sex was a significant predictor of reaction time (β −36.88, 95% CI −60.48 to −13.29); males were slower to respond to correct trials relative to females.

Between groups, children with type 1 diabetes showed an overall reduction in d' (β −0.31, 95% CI −0.54 to −0.09) and accuracy (β −0.02, 95% CI −0.025 to −0.005) across working memory load conditions relative to children in the control group. No difference was observed between the two groups for reaction time (β −5.41, 95% CI −28.86 to 18.45). The interaction of group by working memory load was significant for accuracy (group by 1-back vs. 0-back β −0.028, 95% CI −0.053 to −0.003; group by 2-back vs. 0-back β −0.017, 95% CI −0.044 to 0.011); children with type 1 diabetes were less accurate in the 1-back relative to the 0-back condition compared with control subjects. No significant interactions were observed for working memory load by reaction time or d'. These findings remained generally unchanged when site was added to the model.

Cognitive and Glycemic Measurement

No differences in BRIEF, WISC-IV, or WJ-III scores were observed between groups (Table 1). An average of 257.5 ± 60.7 h of CGM data were collected per participant in the type 1 diabetes group. CGM measures of dysglycemia are presented in Table 1.

fMRI Data

Voxel-based analyses indicated a significant main effect of group in six regions including clusters in the right insula and prefrontal cortex, the parietal and middle temporal gyri, the left cerebellum, and the right thalamus and caudate (Table 3 and Fig. 2*A*). Planned post hoc

Table 1—Characteristics of study participants

	Participants with type 1 diabetes	Control subjects	Significance (*P* value)
General information			
N (female/male)	80 (37/43)	47 (24/23)	0.60
Age (years)	11.8 (10.4, 13.0)	12.0 (10.4, 12.9)	0.55
Cognitive testing (*T* scores)			
WISC-IV Full Scale IQ[a]	114.0 ± 12.2	117.3 ± 13.0	0.14
WISC-IV Working Memory Index[a]	101.1 ± 11.5	103.4 ± 11.5	0.28
BRIEF Global Executive Composite[b]	49.0 (41.0, 55.0)	48.0 (43.0, 53.0)	0.98
BRIEF Working Memory[b]	52.0 (43.0, 60.0)	48.5 (42.3, 56.0)	0.35
WJ-III Spatial Relations[a]	104.5 (99.0, 109.8)	104.5 (98.0, 116.0)	0.64
WJ-III Concept Formation[a]	111.0 (105.0, 122.0)	114.0 (108.0, 126.0)	0.18
Clinical measures			
HbA_{1c} (%)	8.1 ± 1.0	5.2 ± 0.2	<0.01
Age at diabetes onset (years)	5.0 (2.8, 6.5)		
Lifetime averaged HbA_{1c}AUC6%	1.92 ± 0.70		
Blood glucose at scan (mg/dL)	163.8 ± 51.4		
Glucose from CGM (mg/dL)	195.9 ± 37.5		
Glucose CV (mg/dL)	0.41 ± 0.06		
MAGE (mg/dL)	149 ± 28		
AUC180 (mg/dL)	45.3 ± 24.5		
AOCBelow70 (mg/dL)	0.55 (0.21, 0.89)		
DKA history, *n* (%)	22 (27.5)		
SH history, *n* (%)	10 (12.5)		

Data are means ± SD, for variables that are normally distributed, or median (25th, 75th percentile), for variables that are not normally distributed, unless otherwise indicated. IQ, intelligence quotient. [a]Higher scores are better. [b]Lower scores are better.

comparisons indicated that for all clusters, greater modulation of activation by working memory load (i.e., higher slope of activation versus load) was observed in the diabetes relative to the control group (*P* values <0.006) (Fig. 2*B*). (See Table 3 for region-specific significance values.) These findings remained significant after task performance was controlled for (accuracy, reaction time, or *d′*, *P* values <0.05).

Exploratory Analyses: Associations Among Neural, Clinical, and Behavioral Measures

Within the diabetes (but not control) group, increased modulation of neural activation, i.e., higher activation with increasing working memory load, was correlated with better executive function as measured by parent-reported working memory scores on the BRIEF, $r = -0.236$, $P = 0.036$, and by visual inductive/deductive reasoning (involving rule-based categorization and rule switching) as measured by participant assessment on the Concept Formation subtest of the WJ-III, $r = 0.241$, $P = 0.033$. Higher modulation in the diabetes group was also correlated with faster reaction time to correct N-back trials, $r = -0.228$, $P = 0.043$, and an earlier age of type 1 diabetes onset, $r = -0.288$, $P = 0.010$ (Fig. 3). In the control group (but not the group with diabetes), increased modulation was correlated with increased accuracy, $r = 0.351$, $P = 0.017$.

Table 2—Performance on the N-back task

	Participants with type 1 diabetes	Control subjects	95% CI (lower, upper)
Accuracy (% correct)			−0.025, −0.005
0-back	97.6 (96.4, 1.0)	98.8 (96.4, 1.0)	
1-back	95.2 (88.1, 97.6)	97.6 (92.9, 1.0)	
2-back	83.3 (76.2, 88.1)	83.3 (81.0, 88.1)	
Reaction time to correct trials (ms)			−28.864, 18.452
0-back	617.5 (549.9, 733.9)	656.1 (561.9, 764.5)	
1-back	689.9 (593.3, 793.0)	682.5 (587.8, 816.9)	
2-back	781.2 (650.5, 913.6)	747.5 (666.4, 887.3)	
d′			−0.536, −0.090
0-back	4.9 (3.6, 6.2)	4.9 (3.6, 6.2)	
1-back	3.9 (2.9, 4.6)	4.6 (3.3, 6.2)	
2-back	2.3 (1.4, 3.2)	2.8 (1.9, 3.5)	

Group values are presented as median (25th, 75th percentile). Significance of between-group differences across working memory loads is displayed as the bootstrap-based 95% CI with controlling for age and sex. See main text for details on statistical methods.

Table 3—Clusters showing a group difference in neural modulation in voxel-wise fMRI analyses

	MNI coordinates					
Cluster	*x*	*y*	*z*	Cluster size, *k*	Significance, *Z*	Effect size, Cohen *d*
Right insula/IFG	48	18	8	2,379	4.19	0.81
Right MTG/angular gyrus	46	−48	4	1,326	4.51	0.89
Right frontal pole	34	60	−6	969	4.54	0.87
Left cerebellum	−8	−78	−28	749	4.19	0.79
Right thalamus/caudate	14	8	12	265	4.03	0.78
Right superior frontal gyrus	6	38	34	54	3.74	0.71

Coordinates represent voxels with peak magnitude, identified at $Z > 3.1$, with a (corrected) cluster-significance threshold of $P = 0.01$. Effect sizes are noted for cluster peaks. IFG, inferior frontal gyrus; *k*, number of voxels; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus.

No associations were observed in either group between modulation strength (magnitude of activation increase with higher working memory load) and scores on the Working Memory Index of the WISC-IV, the Spatial Relations subtest of the WJ-III, or the BRIEF Global Executive Composite. Further, no significant correlations were observed among modulation strength and blood glucose at scan, history of SH, history of DKA, HbA_{1c}, lifetime averaged $HbA_{1c}AUC_{6\%}$, gluMean, CV, MAGE, AUC180, and AOCBelow70 within the diabetes group. Further, no significant associations were present between glycemic variables or age of onset with N-back task performance or cognitive assessment scores.

Fisher *r*-to-*z* transformations indicated that differences in correlation coefficients for associations between modulation and accuracy, reaction time on the N-back task, and scores on the Working Memory subtest of the BRIEF and the Concept Formation subtest of the WJ-III were not significant between groups (*P* values >0.216). Moreover, correlations between modulation and reaction time did not differ as a function of sex ($r = 0.441$).

DISCUSSION

This study was conducted to investigate the effects of glycemic dysregulation on brain function in a large cohort of children with type 1 diabetes with use of a well-validated working memory task. In both groups, increased activation was associated with greater working memory load in brain areas well recognized for their role in visuospatial working memory, including the frontoparietal cortex, cerebellum, and striatum. Examination of between-group differences indicated that, contrary to our hypotheses, children in the type 1 diabetes group exhibited reduced performance on the N-back task. These behavioral differences were coupled with alterations in activation. Specifically, children with type 1 diabetes exhibited increased modulation (i.e., showed a larger linear increase in activation with higher working memory load) in the right frontoparietal cortices, right caudate, right thalamus, and left cerebellum relative to children without diabetes. Importantly, even after task performance was controlled for, the group differences that we observed in brain activation remained. These findings, taken together with the positive associations that we observed between increased modulation of activation and *1*) performance on the N-back task and *2*) executive function in the type 1 diabetes group, support a model of neural compensation whereby increased activation may help to facilitate normative cognitive functioning in children with diabetes. Given the group differences in performance on the N-back task, however, such compensatory processes appear insufficient to effectively boost performance levels to be equivalent to those of control subjects without diabetes.

To our knowledge, this study is the first to examine the neural correlates of varying working memory load in children with type 1 diabetes. The patterns of increased modulation that we observed are consistent with findings from functional neuroimaging investigations that used similar tasks, showing increased activation in adults with type 1 diabetes (15–17). Thus, compensatory increases

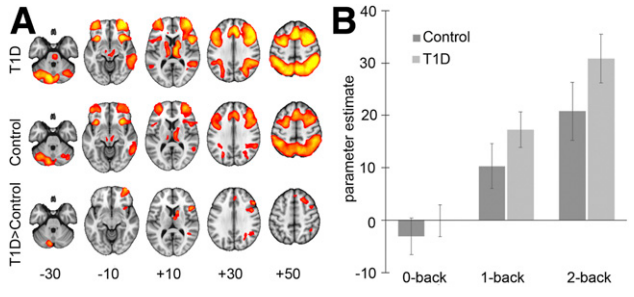

Figure 2—*A*: Regions showing significant modulation of activation by working memory load in children with type 1 diabetes (T1D) (top) and children in the control group (middle) and areas showing a significant increase in modulation in activation among children with type 1 diabetes relative to control subjects (bottom). Values indicate slice numbers. *B*: Mean parameter estimates for each working memory load condition, averaged across significant voxels in between-group analyses. Voxel-wise significance maps are thresholded at $Z > 3.1$, with a cluster significance threshold of $P = 0.01$, corrected for multiple comparisons. Images are presented according to neurological convention (left = left).

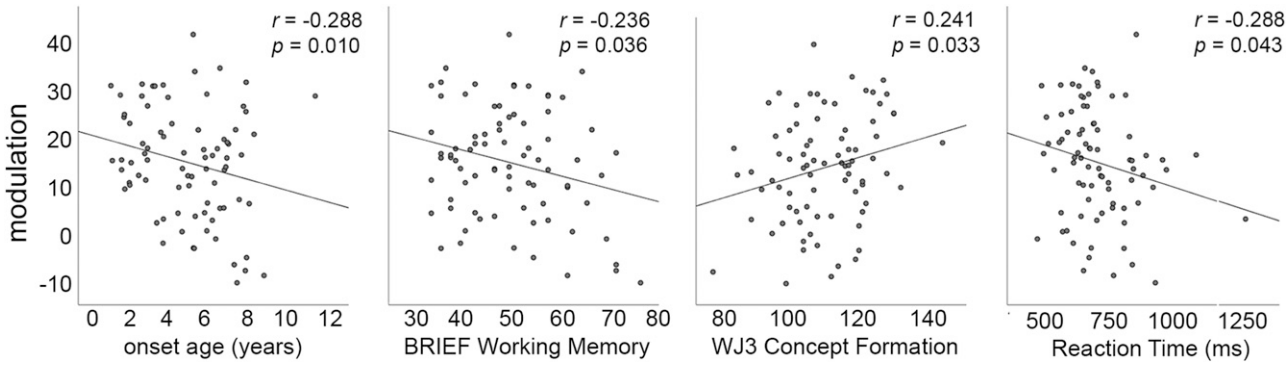

Figure 3—Scatter plots showing associations between modulation strength (adjusted for age, sex, and site) and illness and behavioral and glycemic measures in children with diabetes. Values on the *y*-axis represent the parameter estimate for the modulated regressor adjusted for age, sex, and scan site, centered around the estimate mean. Higher modulation values indicate greater linear increases in activation with higher working memory load. For BRIEF, higher scores indicate worse parent-reported working memory. For WJ-III (WJ3), higher scores indicate better inductive reasoning.

in brain function may arise early in the course of type 1 diabetes and continue into adulthood. A hypothesis of neural compensation may also account for observations of increased resting state functional connectivity that have been observed in adults with type 1 diabetes (32,33). Interestingly, studies of individuals with type 1 diabetes scanned after the onset of microangiopathy show no such increase, suggesting that compensatory elevations in brain function may be a finite phenomenon that is eventually lost with disease progression or poor glycemic control (32). Certainly, there is an important avenue for further work regarding whether children with type 1 diabetes exhibiting poorer treatment adherence and worse disease management over time also show reductions in compensatory activation.

In an earlier DirecNet fMRI investigation, which sampled from a partially overlapping set of children (32%), we observed increased resting state functional connectivity within the dorsal attention network of children with diabetes (34). The magnitude of these increases was positively correlated with cognitive functioning level in children with type 1 diabetes, despite equivalent behavior and cognition between the two groups. In a subsequent report, which also included a partially overlapping sample (84%), hyperactivation in the dorsal anterior cingulate cortex, inferior frontal gyri, cerebellum, and supramarginal gyri, as well as reduced suppression of the posterior default mode network, was observed in the group with type 1 diabetes as they performed a go/no-go task (35). Again, increased activation in task-positive executive control regions was correlated with improvements in executive function in the group with type 1 diabetes, despite equivalent task performance and cognition between the two groups.

Our prior task-based fMRI investigation that used a go/no-go paradigm in a highly overlapping sample of children with type 1 diabetes found no differences in task performance between groups. Therefore, our observation that children with type 1 diabetes performed worse on the N-back task relative to control subjects was unexpected. The reasons for these differences are unclear, but may relate to the individual components of executive function that are uniquely indexed by each task. Extensive research in healthy developing children, for example, shows that working memory and inhibition constitute different, albeit correlated, executive functions (36) that follow different developmental trends (37,38); whereas working memory improves gradually throughout adolescence, substantial gains in inhibitory function generally occur in early childhood (37,38). The N-back task, therefore, may be more sensitive to later subtle alterations in the development of working memory in early adolescence. Certainly, additional studies that examine distinct domains of executive function and their relation to brain function are warranted, particularly since cognitive capabilities are significantly coupled with treatment adherence (39).

In addition to our primary findings, we observed that an earlier age of type 1 diabetes onset (i.e., age at diagnosis) was associated with increased modulation of activation. This finding is in alignment with findings of our prior go/no-go study: that diabetes-related activation differences were significantly more pronounced in children with an earlier onset. These findings lend support to the premise that mounting brain insult could lead to altered neural functioning in type 1 diabetes over time (40). Given our observation that increased modulation in the current study was also associated with improved task performance and working memory function, a correlation between age at diagnosis and brain activation may indicate, more specifically, that children with an earlier disease onset require additional modulation to sufficiently engage in a working memory challenge. Future studies that examine this possibility, as well as whether these differences are mitigated with improved glycemic control early in the course of the disease, are of considerable interest.

Some limitations of our work should be noted. Specifically, exploratory analyses examining association among activation, behavior, dysglycemia, and course of illness were not corrected for multiple comparisons. However, we reduced the number of correlations by using summary metrics of modulation. Second, very little hypoglycemia was experienced by children in our sample. Thus, we were not sufficiently powered to conduct a meaningful analysis of associations between activation and hypoglycemia. Third, although exploratory analyses indicated no association between activation and blood glucose at scan, additional research is needed to independently assess the impact of acute versus chronic dysglycemia on brain dysfunction as observed with fMRI. Finally, because no associations were observed between activation and CGM metrics, the mechanisms underlying increased modulation in the group with type 1 diabetes, whether inflammatory processes, subtle microvascular disease, development of advanced glycation end products, etc., remain to be determined.

In conclusion, we present differences in functional brain activation in young children with type 1 diabetes compared with age- and sex-matched children without diabetes. Our results suggest that working memory–related increases in activation—observed previously in adults with type 1 diabetes—may start early in the course of the disease and play a compensatory role, helping to support normative behavioral performance levels in children with diabetes. The associations that we observed between hypermodulation and working memory performance further support this interpretation. However, such increases appear to be insufficient in raising working memory performance to be equivalent to that of healthy children, as indicated by group differences in task accuracy and d'. Finally, we observed that patterns of increased modulation were significantly more pronounced in children with an earlier age of diabetes onset. Future work that seeks to extend these findings through examining whether increased modulation of activation is lost with disease progression and/or changes as a function of improved glycemic control would be helpful in clarifying the influence of type 1 diabetes on brain function.

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Author Contributions. L.C.F.-R., G.T., N.M., A.C., T.A., M.T., N.H.W., S.A.W., K.E., H.S., P.K.M., and A.L.R. reviewed and edited the manuscript and approved the final version. G.T., P.K.M., T.A., N.M., S.A.W., N.H.W., A.C., and K.E. acquired the data. P.K.M., K.E., and G.T. organized the data. L.C.F.-R., G.T., and H.S. analyzed the data. N.M. and A.L.R. designed the study. L.C.F.-R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

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