



# Acute Hyperglycemia and Spatial Working Memory in Adolescents With Type 1 Diabetes

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## OBJECTIVE

To investigate the effect of acute hyperglycemia on brain function in adolescents with type 1 diabetes (T1D).

## RESEARCH DESIGN AND METHODS

Twenty participants with T1D (aged  $14.64 \pm 1.78$  years) and 20 age-matched healthy control subjects (aged  $14.40 \pm 2.82$  years) performed two functional MRI sessions. Participants with T1D performed the first scanning session under euglycemic and the second under hyperglycemic clamp (20 mmol/L [360 mg/dL]).

## RESULTS

Lower spatial working memory (sWM) capacity during acute hyperglycemia and significant differences in activation of regions of interest during different stages of the sWM task ( $P = 0.014$ ) were observed.

## CONCLUSIONS

Acute hyperglycemia negatively affected sWM capacity in adolescents with T1D, which is relevant for daily functioning and academic performance.

Type 1 diabetes (T1D) has an impact on the structure and function of the brain in children and adults (1,2). Basic intelligence, psychomotor processing speed, mental flexibility, and attention are noted to be permanently reduced (1,3). Hyperglycemia may have more deleterious effects on the brain than hypoglycemia (1,4).

Spatial working memory (sWM) is decisive in achieving better academic performance (5). We investigated the effects of acute hyperglycemia on sWM in adolescents with T1D.

## RESEARCH DESIGN AND METHODS

The primary outcome of this open-label clinical trial (NCT03188757, National Medical Ethics Committee 0120–476/2017/2) was the difference in sWM capacity during acute hyperglycemia compared with euglycemia in adolescents with T1D.

Inclusion criteria were age 11–19 years, duration of T1D 5–10 years, and no severe hypoglycemic episode or diabetic ketoacidosis within the previous year. The control group consisted of age-matched healthy adolescents, not related to participants with T1D.

After an overnight stay to maintain stable glycemia, participants with T1D started with an intravenous euglycemic clamp, during which functional MRI with an sWM task and MRI spectroscopy were performed. Capillary blood glucose concentration was measured (CONTOUR NEXT; Ascensia, Parsippany, NJ) every 15 min and maintained between 5 and 10 mmol/L (90–180 mg/dL). Afterward, the blood glucose level was

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raised by an intravenous glucose bolus, and a hyperglycemic clamp (6) was maintained between 15 and 25 mmol/L (270–450 mg/dL) for 2 h, during which participants repeated the scanning protocol.

To control for the effects of learning and fatigue, healthy control subjects followed the same experimental protocol, but without any manipulation of glycemia.

Participants were familiarized with the spatial variation of the Sternberg item-recognition task (7) prior to the scanning sessions. Group differences and the effect of induced hyperglycemia on sWM capacity estimates were assessed using a two-way mixed-design ANOVA with within-subject factor session (first vs. second session) and between-subject factor group (participants with T1D vs. healthy control subjects). The analysis was performed using the ez-package (8) separately for sWM loads of two and four items.

Neuroimaging data were acquired with an Achieva 3.0T TX scanner (Philips, Best, the Netherlands). T1- and T2-weighted high-resolution images were acquired, and in each functional session, three T2\*-weighted blood oxygen level-dependent images concurrent with sWM task performance, followed by spectroscopy scan using SV-PRESS sequence, were obtained.

Initial image preprocessing followed the Human Connectome Project minimal preprocessing pipeline (9). Further analyses were conducted using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu>) (10) and in-house code using MATLAB 2014a (<https://mathworks.com>) and R (11) software packages.

The analysis of functional data was performed on a priori selected regions of interest (ROIs) (frontal eye fields, supplementary motor area, anterior insula, anterior intraparietal area, medial intraparietal area, inferior frontal junction, dorsolateral prefrontal cortex, and medial temporal lobe) (8). The selected ROIs are involved in the spatial information forming and its maintenance and executive control (12,13). Separate estimates of brain activation during encoding, delay, and response phase for each session and sWM load were obtained using a general linear model. Individual activation estimates for each ROI were then submitted to a second-level analysis. The effects of interest on mean ROI

responses were investigated using a mixed-effects ANOVA with within-subject factors session (first vs. second), load (2 vs. 4), task phase (encoding, delay, and response), hemisphere (left vs. right), ROI, and a between-subject factor group (participants with T1D vs. healthy control subjects).

In the frontal cortex, ratios of magnetic resonance relaxation-corrected surface areas of *N*-acetyl aspartate, choline, and creatine were compared within each group and between the groups after functional MRI sessions. The Wilcoxon rank-sum test (between groups) and Wilcoxon signed-rank test (paired difference inside groups between the first and second measurements) were used; correlation between the blood glucose concentration and metabolites was assessed with linear mixed-effects model, all using R.

## RESULTS

Twenty adolescents with T1D (mean  $14.64 \pm 1.78$  years of age; 10 female; mean T1D duration  $8.00 \pm 2.45$  years) and 20 healthy age-matched control subjects (mean  $14.4 \pm 2.82$  years of age; 15 female) completed the study protocol. Fifteen adolescents with T1D and 19 control subjects were included in the final analysis (6 were excluded due to motion-related artifacts) (Supplementary Table 1 and CONSORT flow chart in Supplementary Material). The average blood glucose level was  $7.6 \pm 2.0$  mmol/L ( $137 \pm 36$  mg/dL) during the euglycemic clamp and  $20.1 \pm 2.4$  mmol/L ( $362 \pm 43$  mg/dL) during the hyperglycemic clamp.

Behavioral analysis of the number of retained positions in the sWM task at load four revealed a significant group  $\times$  session interaction ( $P = 0.048$ ), reflecting a robust decrease in the estimated number of successfully retained positions in adolescents with T1D versus an increase in healthy control subjects from session 1 to session 2 (Supplementary Fig. 1).

Analysis of brain activation on a priori ROI (Fig. 1A) revealed a significant ( $P = 0.014$ ) group  $\times$  session interaction, reflecting a decrease of activation in the second session from overall higher values in adolescents with T1D as compared with only moderate increase in activation in healthy control subjects (Fig. 1B). A significant ( $P = 0.016$ ) group  $\times$  session  $\times$  task phase  $\times$  side interaction indicated more specific

differences in the effect of the session between groups (Fig. 1C). Separate analyses for each combination of task phase (encoding, delay, and response) and hemisphere (left vs. right) revealed significant group  $\times$  session interaction during response phase in left ( $P = 0.046$ ) and right ( $P = 0.016$ ) hemisphere, as shown in the response time course for the two groups averaged across ROIs (Fig. 1D).

Spectroscopy revealed a significant decrease in of *N*-acetyl aspartate, choline, and creatine ( $P < 0.01$ ,  $P < 0.005$ , and  $P < 0.01$ , respectively) at the end of the hyperglycemic clamp. This decrease correlated significantly ( $P < 0.01$ ,  $P < 0.01$ , and  $P < 0.05$ , respectively) with the increase in blood glucose concentrations. The ratios among the metabolites did not change significantly. No significant change in metabolite levels were observed in the control group.

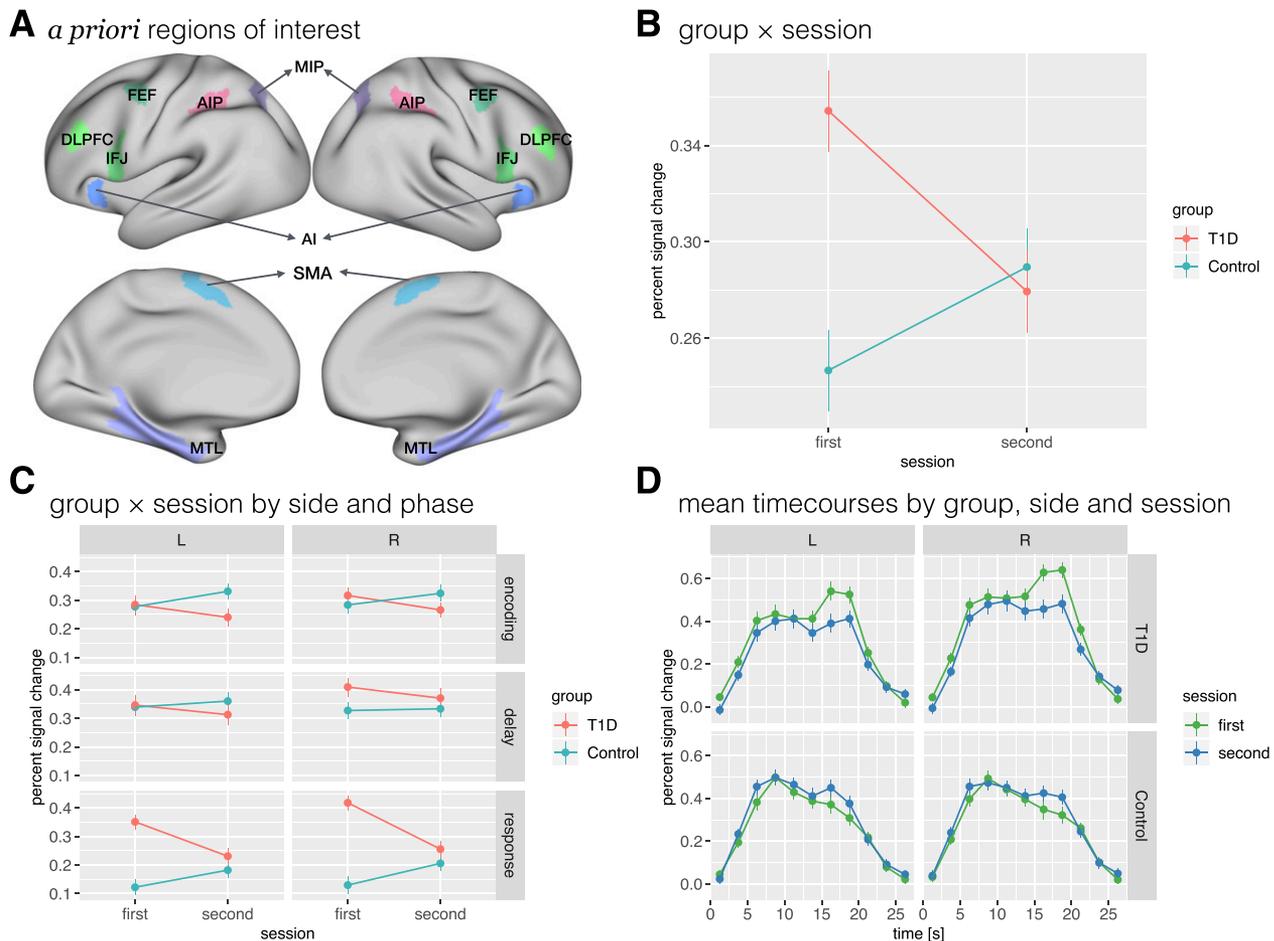
## CONCLUSIONS

The significantly reduced sWM capacity in adolescents with T1D during acute hyperglycemia observed in our study substantiates previous observations showing a decrease in intelligence quotient scores in children with T1D (4) and impaired WM in adults with T2D, both during acute hyperglycemia (14).

Our study is the first to suggest a direct effect of acute hyperglycemia on sWM. Significantly higher overall brain activation in adolescents with T1D compared with healthy control subjects during the first session reversed to an overall decrease of activation in the second session during hyperglycemia. The increased brain activity during response phase could be a compensatory mechanism for less efficient encoding of stimuli (12). During high sWM load, a failure to engage this compensatory mechanism, observed as a significant drop in activation, could explain the reduced sWM capacity during hyperglycemia.

The overall significant decrease of metabolites in the frontal cortex during hyperglycemia could be related to a concomitant increase in local water content. Hyperglycemia affects the blood-brain barrier and may contribute to clinically silent water content changes in brain regions (15). No changes were observed in the control group.

Our study has limitations: it is single center, included a limited number of participants, and used restricted magnetic



**Figure 1**—Differences in brain activation as assessed by functional MRI during the performance of the sWM task between adolescents with T1D and healthy control subjects. *A* shows *a priori* ROIs. *B* presents the change of activation in ROIs between first and second session in the group with T1D and the healthy control group. *C* presents change of activation in ROIs between the first and second session in the group with T1D and the healthy control group shown separately for each phase of working memory task and hemisphere. *D* presents mean time courses of activation in ROIs by group, hemisphere, and session, showing higher levels of activation in participants with T1D during euglycemia and a decrease of activation during hyperglycemia. AI, anterior insula; AIP, anterior intraparietal area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; IFJ, inferior frontal junction; L, left; MIP, medial intraparietal area; MTL, medial temporal lobe; R, right; SMA, supplementary motor area.

resonance acquisitions. The results could be related to other factors than acute hyperglycemia or T1D: changes in the water content or diabetic ketoacidosis at T1D onset (present in 6 out of 20 participants).

sWM enables easily accessible information maintenance over brief time periods and is crucial for goal-directed behavior (12). The impact of acute hyperglycemia on sWM has a direct clinical implication for school performance and other cognitive challenges in this vulnerable population with T1D.

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**Duality of Interest.** G.R. consults for and holds equity in BlackThorn Therapeutics. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** J.Š.O. contributed to conception and design of the study, data acquisition, analysis, and interpretation, and drafting of the manuscript and gave final approval for submission. A.S.O., A.V., D.Š., G.R., and T.B.

contributed to conception and design of the study and analysis and interpretation of data, made critical revisions for important intellectual content, and gave final approval for submission. K.D., N.B., and M.A.S. contributed to data acquisition, made critical revisions for important intellectual content, and gave final approval for submission. T.B. 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.

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